

**A Concise Total Synthesis of (–)-Quinocarcin via Aryne Annulation**

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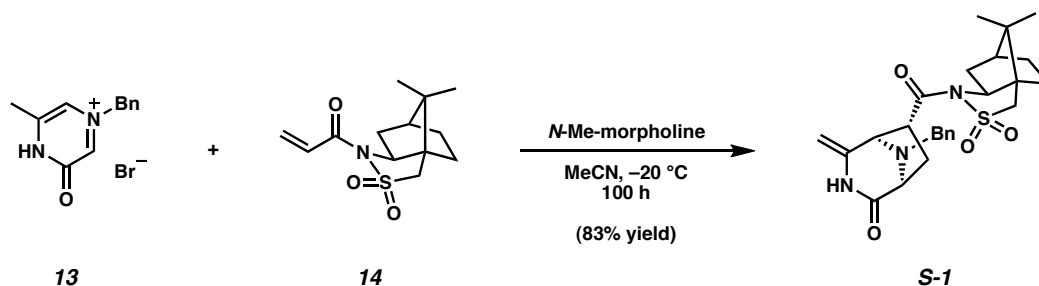
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## Materials and Methods

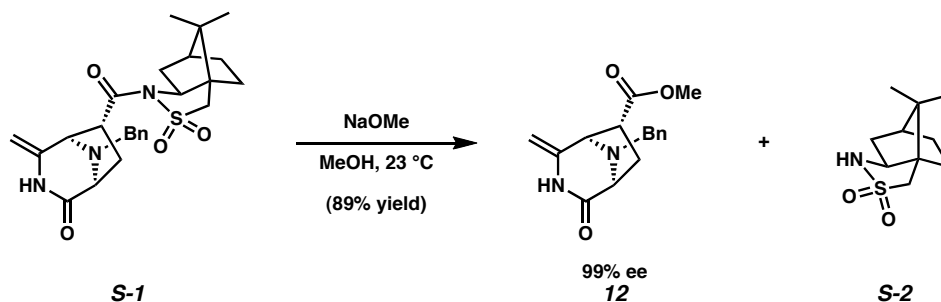
Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKA Mag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) using a Chiralcel OD-H column (250 mm x 4.6 mm, 5  $\mu$ m particle size, 2.0 mL/min flow rate). Preparatory reverse-phase HPLC was performed on a Waters HPLC with a Waters Delta-Pak column (100 mm x 2 mm, 15  $\mu$ m particle size, 1.5 mL/min flow rate) equipped with a guard, employing a variable gradient of methanol and water.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to  $\text{Me}_4\text{Si}$  ( $\delta$  0.0). Data for  $^1\text{H}$  NMR spectra are reported as follows: chemical shift ( $\delta$  ppm) (multiplicity, coupling constant (Hz), integration). Data for  $^{13}\text{C}$  NMR spectra are reported in terms of chemical shift relative to  $\text{Me}_4\text{Si}$  ( $\delta$  0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption ( $\text{cm}^{-1}$ ). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Optical rotations were measured on a Jasco P-1010 polarimeter using a 100 mm path-length cell.

## Experimental Procedures



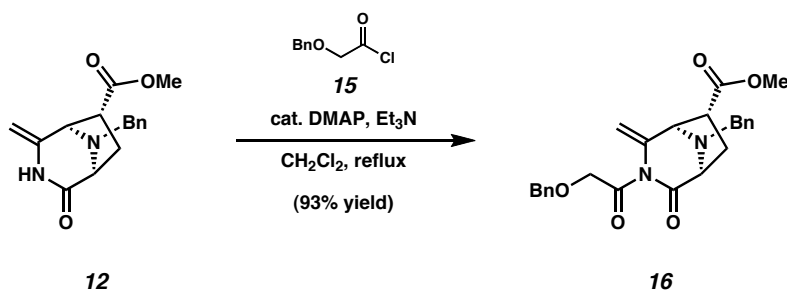
**Diazabicyclic S-1.**<sup>1,2</sup> A flame-dried 1 L round-bottomed flask equipped with a stir bar was charged with oxidopyrazinium bromide **13** (12.70 g, 45.2 mmol) and acetonitrile (250 mL). The suspension was cooled to  $-20\text{ }^{\circ}\text{C}$  in a Thermo Scientific NESLAB CB-80 cold bath. *N*-methylmorpholine (14.9 mL, 136 mmol) was added via syringe and the mixture was stirred until all solids had dissolved (10 min). A solution of acrylamide **14** (14.57 g, 54.1 mmol) in acetonitrile (350 mL) was then added and the reaction was maintained at  $-20\text{ }^{\circ}\text{C}$  for 100 h. The reaction was then diluted cold in EtOAc (400 mL) and washed with water (2 x 300 mL). The combined aqueous layers were extracted with EtOAc (2 x 200 mL) and the combined organic layers were washed with brine (400 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The resulting crude orange-yellow solid was filtered through a plug of silica ( $\text{CH}_2\text{Cl}_2 \rightarrow 75:25$  EtOAc/hexanes) to remove orange baseline material. Solvent was removed under reduced pressure to afford an off-white solid.<sup>3</sup> The crude solid was dissolved in a minimum amount of  $\text{CH}_2\text{Cl}_2$  (240 mL), and to this solution was added hexanes (300 mL) while swirling until the first crystals were visible. The solution was then allowed to stand at  $23\text{ }^{\circ}\text{C}$  for 8 h. Filtration under vacuum provided diazabicyclic **S-1** (14.85 g, 70% yield) as a white solid. The mother liquor was concentrated and the residue was resubmitted to recrystallization to provide additional diazabicyclic **S-1** (2.75 g, 13% yield — 83% combined yield) as a white solid.  $R_f = 0.38$  (50:50 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (br s, 1H), 7.31–7.21 (comp m, 5H), 4.38 (d,  $J = 1.2$  Hz, 1H), 4.32 (d,  $J = 1.2$  Hz, 1H), 3.94 (d,  $J = 12.8$  Hz, 1H), 3.89 (dd,  $J = 7.8, 4.6$  Hz, 1H), 3.74 (d,  $J = 7.8$  Hz, 1H), 3.68 (s, 1H), 3.59 (dd,  $J = 9.0, 3.9$

Hz, 1H), 3.57 (d,  $J = 12.8$  Hz, 1H), 3.41 (s, 2H), 3.06 (ddd,  $J = 13.4, 7.8, 3.9$  Hz, 1H), 2.15 (dd,  $J = 13.4, 9.0$  Hz, 1H), 2.06 (dd,  $J = 13.9, 7.8$  Hz, 1H), 1.91–1.84 (comp m, 3H), 1.82 (dd,  $J = 4.2, 3.7$  Hz, 1H), 1.43–1.32 (comp m, 2H), 0.92 (s, 3H), 0.75 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 171.3, 139.2, 138.2, 128.8, 128.5, 127.5, 94.0, 65.8, 63.4, 63.3, 53.3, 52.1, 49.2, 48.6, 47.9, 44.8, 38.5, 33.0, 31.3, 26.6, 20.8, 20.0; IR (Neat Film, NaCl) 3199, 2960, 1688, 1654, 1455, 1329, 1213, 1134, 853  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{25}\text{H}_{32}\text{N}_3\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 470.2108, found 470.2136;  $[\alpha]_{\text{D}}^{22} +100.72^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).



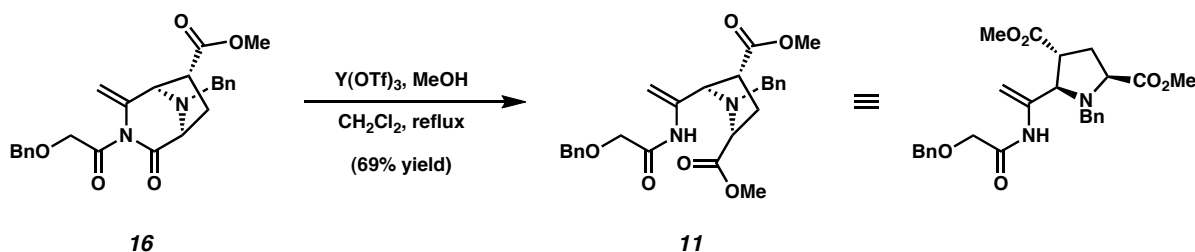
**Ester 12.** A flame-dried 500 mL round-bottomed flask equipped with a stir bar was charged with a 60% w/w suspension of NaH in mineral oil (1.32 g, 33.0 mmol). Methanol (200 mL) was slowly added with stirring at 23 °C under argon. **Warning:** vigorous gas evolution. The suspension was stirred until all solids had dissolved (15 min). A solution of diazabicyclic **S-1** (5.07 g, 10.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was then added, and the reaction was maintained at 23 °C for 20 min. The reaction was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (250 mL) and extracted into EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The residue was purified via flash chromatography over silica gel (25:75  $\rightarrow$  30:70 EtOAc/hexanes) to afford methyl ester **12** (2.75 g, 89% yield) as a white solid and sultam **S-2** (1.74 g, 75% yield) as a white crystalline solid.  $R_f = 0.45$  (50:50 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35 (br s, 1H), 7.35–7.29 (comp m, 4H), 7.28–7.24 (m, 1H), 4.33 (d,  $J = 1.2$  Hz, 1H), 4.19 (d,  $J = 1.2$ ,

1H), 4.02 (s, 1H), 3.82 (d,  $J = 13.4$  Hz, 1H), 3.74 (s, 3H), 3.73 (d,  $J = 13.4$  Hz, 1H), 3.62 (d,  $J = 7.3$  Hz, 1H), 3.02 (dd,  $J = 9.8, 5.6$  Hz, 1H), 2.66 (ddd,  $J = 13.2, 7.3, 5.6$  Hz, 1H), (dd,  $J = 13.2, 9.8$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6, 171.6, 141.3, 137.9, 128.7, 128.6, 127.6, 91.7, 63.3, 62.5, 52.6, 52.5, 48.4, 33.5; IR (Neat Film, NaCl) 3202, 2953, 1737, 1684, 1656, 1454, 1318, 1200, 850  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 287.1396, found 287.1390;  $[\alpha]_{\text{D}}^{26} -23.66^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ). Analytical chiral SFC assay: Chiralcel OD-H column, 10:90 2-propanol: $\text{CO}_2$ , 2.0 mL/min,  $\lambda = 254$  nm, 40  $^\circ\text{C}$  isothermal method over 20 min. Racemic **12**:  $t_{\text{fast}} = 11.31$  min ((-)-**12**, 49.9%),  $t_{\text{slow}} = 11.89$  min ((+)-**12**, 50.1%). Enantio-enriched **12**:  $t_{\text{fast}} = 11.39$  min ((-)-**12**, >99%) (the trace corresponding to (+)-**12** was below the threshold of detection).



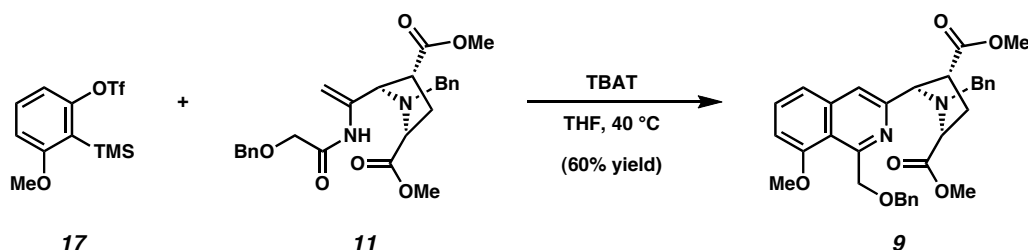
**Imide 16.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and a reflux condenser was charged with benzyloxycarbonyl chloride (8.76 g, 52.8 mmol) and  $\text{CH}_2\text{Cl}_2$  (140 mL). To this solution was added oxalyl chloride (4.53 mL, 51.9 mmol) and  $N,N$ -dimethylformamide (0.205 mL, 2.65 mmol). **Warning:** vigorous gas evolution. The reaction was maintained at 23  $^\circ\text{C}$  until bubbling had ceased (45 min). A solution of ester **12** (5.00 g, 17.5 mmol), triethylamine (7.9 mL, 56.7 mmol), and 4-dimethylaminopyridine (0.325 g, 2.66 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) was then added dropwise via syringe over 5 min. The reaction was heated to 40  $^\circ\text{C}$  and maintained for 30 h. After cooling to room temperature, the solution was diluted in  $\text{CH}_2\text{Cl}_2$  (200 mL) and washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (200 mL), water (200 mL), and brine (200 mL). The organic layer was dried over  $\text{MgSO}_4$  and

concentrated under reduced pressure. The crude orange residue was purified via flash chromatography over silica gel (15:85  $\rightarrow$  25:75 EtOAc/hexanes) to afford imide **16** (7.06 g, 93% yield) as a colorless oil.  $R_f$  = 0.47 (30:70 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.34 (comp m, 4H), 7.34–7.29 (comp m, 4H), 7.29–7.24 (comp m, 2H), 5.25 (d,  $J$  = 1.2 Hz, 1H), 4.65 (s, 2H), 4.59 (d,  $J$  = 1.2 Hz, 1H), 4.56 (d,  $J$  = 16.8 Hz, 1H), 4.49 (d,  $J$  = 16.8 Hz, 1H), 4.04 (s, 1H), 3.77 (d,  $J$  = 4.9 Hz, 2H), 3.74 (s, 3H), 3.68 (d,  $J$  = 7.1 Hz, 1H), 3.04 (dd,  $J$  = 9.8, 6.0 Hz, 1H), 2.62 (ddd,  $J$  = 13.4, 7.1, 6.0 Hz, 1H), 2.26 (dd,  $J$  = 13.4, 9.8 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  175.9, 173.4, 172.1, 139.2, 137.4, 137.2, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 99.8, 74.0, 72.9, 65.2, 64.7, 52.7, 52.7, 47.5, 32.7; IR (Neat Film, NaCl) 2952, 1736, 1634, 1454, 1200, 1117, 1028  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$ : 435.1920, found 435.1930;  $[\alpha]_D^{21}$   $-51.53^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).



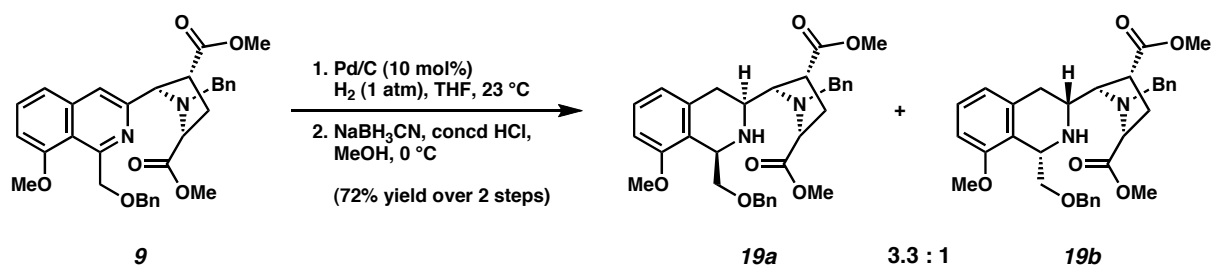
***N*-acyl enamine 11.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and reflux condenser was charged with  $\text{Y}(\text{OTf})_3$  (2.59 g, 4.83 mmol) and  $\text{CH}_2\text{Cl}_2$  (120 mL). The suspension was heated to 40  $^\circ\text{C}$  and a solution of imide **16** (2.05 g, 4.72 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) was added. The mixture was maintained at 40  $^\circ\text{C}$  for 1 h, at which point MeOH (1.35 mL, 33.3 mmol) was added via syringe. The suspension immediately cleared and stirring was continued at 40  $^\circ\text{C}$  for an additional 30 min. After cooling to room temperature, the reaction was concentrated to a cloudy yellow oil containing yttrium salts, which was suspended in a minimum amount of  $\text{CH}_2\text{Cl}_2$  (12 mL) and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified via flash chromatography over silica gel (25:75  $\rightarrow$  40:60 EtOAc/hexanes) to yield *N*-acyl enamine **11** (1.52 g,

69% yield) as a pale yellow oil.  $R_f = 0.70$  (50:50 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.18 (br s, 1H), 7.43 (d,  $J = 6.6$  Hz, 2H), 7.39 (dd,  $J = 7.2, 6.6$  Hz, 2H), 7.34, (tt,  $J = 7.2, 1.5$  Hz, 1H), 7.29–7.22 (comp m, 5H), 6.01 (s, 1H), 4.76 (d,  $J = 1.2$  Hz, 1H), 4.75 (d,  $J = 12.4$  Hz, 1H), 4.71 (d,  $J = 12.4$  Hz, 1H), 4.06 (s, 2H), 3.97 (d,  $J = 13.7$  Hz, 1H), 3.69 (s, 3H), 3.65 (d,  $J = 9.0$  Hz, 1H), 3.60 (d,  $J = 13.7$  Hz, 1H), 3.56 (dd,  $J = 9.5, 4.2$  Hz, 1H), 3.40 (s, 3H), 3.09 (dd,  $J = 9.5, 8.8$  Hz, 1H), 2.33 (dt,  $J = 12.9, 9.8$  Hz, 1H), 2.13 (ddd,  $J = 12.7, 8.3, 4.2$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.4, 173.2, 169.5, 137.4, 137.3, 136.8, 129.7, 128.8, 128.5, 128.3, 128.2, 127.8, 101.7, 73.7, 72.2, 70.0, 63.2, 56.4, 52.4, 52.0, 47.6, 33.1; IR (Neat Film, NaCl) 3316, 2951, 1737, 1696, 1512, 1454, 1436, 1201, 1174, 1028  $\text{cm}^{-1}$ ; HRMS (ES+)  $m/z$  calc'd for  $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 467.2182, found 467.2188;  $[\alpha]_{\text{D}}^{25} -29.78^\circ$  (c 1.0,  $\text{CHCl}_3$ ).



**Isoquinoline 9.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and reflux condenser was charged with tetra-*n*-butylammonium difluorotriphenylsilicate (5.45 g, 10.1 mmol) and THF (120 mL). A solution of *N*-acyl enamine **11** (2.35 g, 5.04 mmol) in THF (50 mL) was added at 23 °C, followed by silylaryl triflate **17**<sup>4</sup> (3.31 g, 10.1 mmol). The reaction was heated to 40 °C and maintained for 15 h, then cooled to room temperature and concentrated under reduced pressure. The yellow residue was purified via flash chromatography over silica gel (15:85 → 25:75 EtOAc/hexanes) to afford isoquinoline **9** (1.68 g, 60% yield) as a pale yellow oil.  $R_f = 0.65$  (50:50 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (s, 1H), 7.55 (dd,  $J = 8.1, 7.8$  Hz, 1H), 7.44 (d,  $J = 7.6$  Hz, 2H), 7.34 (dd,  $J = 7.8, 7.1$  Hz, 2H), 7.32–7.25 (comp m, 4H), 7.22 (dd,  $J = 7.6, 7.1$  Hz, 2H), 7.15 (t,  $J = 7.3$  Hz,

1H), 6.90 (d,  $J = 7.8$  Hz, 1H), 5.32 (d,  $J = 12.5$  Hz, 1H), 5.29 (d,  $J = 12.5$  Hz, 1H), 4.78 (d,  $J = 11.7$  Hz, 1H), 4.68 (d,  $J = 11.7$  Hz, 1H), 4.52 (d,  $J = 6.1$  Hz, 1H), 4.04 (d,  $J = 13.4$  Hz, 1H), 3.96 (s, 3H), 3.79 (d,  $J = 13.4$  Hz, 1H), 3.77 (dd,  $J = 9.5, 7.6$  Hz, 1H), 3.61 (s, 3H), 3.51 (s, 3H), 3.31 (dt,  $J = 8.3, 6.1$  Hz, 1H), 2.44 (ddd,  $J = 12.7, 8.3, 6.1$  Hz, 1H), 2.26 (ddd,  $J = 12.7, 8.1, 7.8$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.8, 174.5, 157.7, 156.4, 154.2, 140.0, 139.2, 137.9, 130.4, 129.8, 128.5, 128.4, 128.2, 127.6, 127.4, 120.3, 118.0, 106.7, 75.2, 73.0, 72.7, 65.3, 58.1, 55.9, 52.2, 51.9, 50.6, 45.0, 32.9; IR (Neat Film, NaCl) 2950, 1736, 1733, 1619, 1566, 1454, 1361, 1201, 1171  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 555.2490, found 555.2497;  $[\alpha]_D^{24} -8.21^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).



**Tetrahydroisoquinolines 19a and 19b.** A flame-dried 10 mL round-bottomed flask equipped with a stir bar was charged with 10% w/w palladium on carbon (0.019 g, 0.018 mmol) followed by a solution of isoquinoline **9** (0.100 g, 0.180 mmol) in THF (3.6 mL). The flask was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 6 h, then filtered through a plug of silica with 30:70 EtOAc/hexanes. Removal of the solvents under vacuum provided a 3.3:1 mixture of dihydroisoquinolines **18a** and **18b**<sup>5</sup> (not shown) (0.082 g), which was carried on without further purification. A flame-dried 5 mL round-bottomed flask equipped with a stir bar was charged with dihydroisoquinolines **18a** and **18b** (0.082 g, 0.148 mmol) in methanol (2.9 mL), and the solution was cooled to 0 °C. Concentrated hydrochloric acid (0.018 mL, 0.216 mmol) was added via syringe followed by  $\text{NaBH}_3\text{CN}$  (0.046 g, 0.732 mmol) added in portions, allowing for bubbling to subside. The reaction was maintained at 0 °C for 15 min, and then quenched with saturated aqueous  $\text{NaHCO}_3$  (1.5

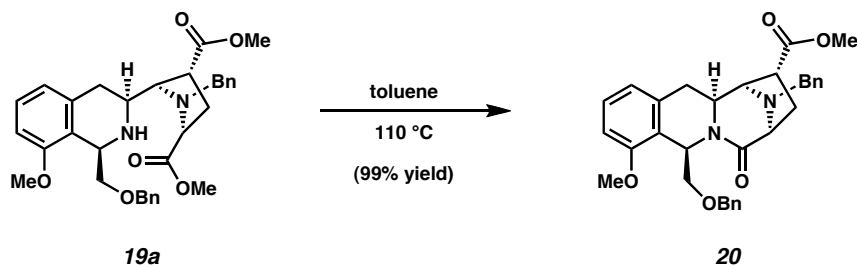


mL) followed by  $\text{CH}_2\text{Cl}_2$  (1.5 mL). The cloudy white mixture was vigorously stirred for 5 min, then 0.2 N NaOH was added dropwise until the mixture cleared (6 drops). The biphasic mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The yellow residue was purified via flash chromatography over silica gel (15:85 EtOAc/hexanes) to yield tetrahydroisoquinoline **19a** (0.055 g, 55% yield over 2 steps) as a clear colorless oil and tetrahydroisoquinoline **19b** (0.017 g, 17% yield over 2 steps) as a clear colorless oil.

**Tetrahydroisoquinoline 19a.**  $R_f$  = 0.38 (30:70 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (d,  $J$  = 7.3 Hz, 2H), 7.36–7.29 (comp m, 4H), 7.29–7.23 (comp m, 3H), 7.21 (dd,  $J$  = 7.3, 7.1 Hz, 1H), 7.11 (t,  $J$  = 7.8 Hz, 1H), 6.72 (d,  $J$  = 7.6 Hz, 1H), 6.68 (d,  $J$  = 8.3 Hz, 1H), 4.66 (d,  $J$  = 12.2 Hz, 1H), 4.59 (d,  $J$  = 12.2 Hz, 1H), 4.47 (d,  $J$  = 7.1 Hz, 1H), 4.17 (dd,  $J$  = 8.8, 2.2 Hz, 1H), 3.99 (d,  $J$  = 13.9 Hz, 1H), 3.81 (d,  $J$  = 13.9 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.63 (dd,  $J$  = 8.3, 7.8 Hz, 1H), 3.46–3.33 (comp m, 4H), 3.38 (s, 3H), 2.98 (ddd,  $J$  = 11.2, 2.9, 2.7 Hz, 1H), 2.65 (dd,  $J$  = 14.7, 11.2 Hz, 1H), 2.55 (dd,  $J$  = 14.7, 2.7 Hz, 1H), 2.35 (ddd,  $J$  = 12.5, 7.1, 3.8 Hz, 1H), 2.27 (ddd,  $J$  = 12.7, 9.0, 8.8 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  176.1, 174.4, 157.1, 139.4, 139.1, 138.7, 129.3, 128.4, 128.3, 127.8, 127.5, 127.4, 127.1, 124.4, 121.8, 108.2, 75.2, 73.1, 72.0, 66.8, 59.1, 55.3, 53.6, 53.4, 52.3, 51.8, 45.0, 42.9, 34.5, 34.0; IR (Neat Film, NaCl) 2949, 1734, 1731, 1584, 1470, 1255, 1198, 1170, 1074  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 559.2803, found 559.2814;  $[\alpha]_D^{23}$   $-52.71^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).

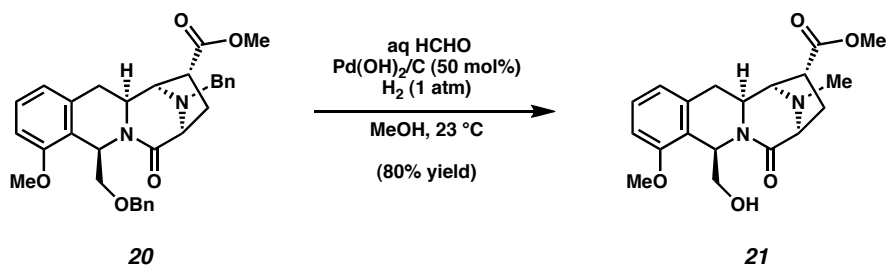
**Tetrahydroisoquinoline 19b.**  $R_f$  = 0.18 (30:70 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (d,  $J$  = 7.6 Hz, 2H), 7.38 (t,  $J$  = 7.6 Hz, 2H), 7.38–7.34 (comp m, 2H), 7.30 (t,  $J$  = 7.3 Hz, 1H), 7.19–7.14 (comp m, 3H), 7.12 (t,  $J$  = 7.8 Hz, 1H), 6.71 (d,  $J$  = 7.8 Hz, 1H), 6.65 (d,  $J$  = 8.1 Hz, 1H), 4.72 (d,  $J$  = 12.2 Hz, 1H), 4.68 (d,  $J$  = 12.2 Hz, 1H), 4.62 (dd,  $J$  = 9.5, 2.2 Hz, 1H), 4.03 (d,  $J$  = 13.4 Hz,

1H), 3.79 (d,  $J = 13.4$  Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67–3.56 (comp m, 3H), 3.60 (d,  $J = 9.3$  Hz, 1H), 3.39–3.32 (comp m, 2H), 3.38 (s, 3H), 3.30 (app dt,  $J = 8.1, 7.1$  Hz, 1H), 2.60 (d,  $J = 7.6$  Hz, 2H), 2.35–2.21 (comp m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  176.2, 174.3, 156.6, 139.2, 138.2, 136.9, 129.8, 128.5, 128.3, 127.8, 127.6, 127.4, 123.8, 121.6, 107.7, 72.8, 71.5, 69.4, 66.8, 59.2, 55.4, 52.3, 51.8, 47.4, 42.7, 34.1, 32.4; IR (Neat Film, NaCl) 2949, 1733, 1588, 1454, 1257, 1198, 1171, 1074  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 559.2803, found 559.2825;  $[\alpha]_D^{21} -17.00^\circ$  ( $c$  0.5,  $\text{CHCl}_3$ ).



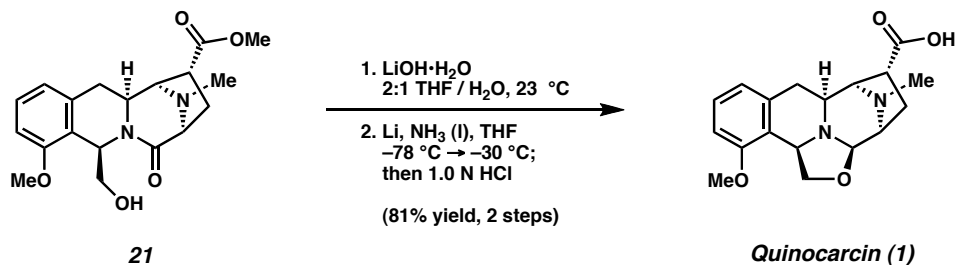
**Lactam 20.** A flame-dried 20 mL scintillation vial equipped with a stir bar was charged with tetrahydroisoquinoline **19a** (0.075 g, 0.135 mmol) in toluene (5.4 mL). The vial was sealed with a teflon cap and the reaction was heated to 110 °C for 24 h. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. Purification via flash chromatography over silica gel (25:75 EtOAc/hexanes) provided tetracyclic lactam **20** (0.071 g, 99% yield) as a pale yellow oil.  $R_f = 0.61$  (50:50 EtOAc/hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.22 (comp m, 9H), 7.21 (t,  $J = 8.0$  Hz, 1H), 7.07 (dd,  $J = 7.6, 2.4$  Hz, 1H), 6.79 (d,  $J = 8.3$  Hz, 1H), 6.74 (d,  $J = 7.3$  Hz, 1H), 5.64 (t,  $J = 2.2$  Hz, 1H), 4.32 (d,  $J = 12.0$  Hz, 1H), 4.29 (d,  $J = 12.0$  Hz, 1H), 4.25 (dd,  $J = 9.5, 3.2$  Hz, 1H), 3.79 (s, 3H), 3.76 (dd,  $J = 12.4, 2.2$  Hz, 1H), 3.73 (s, 3H), 3.72 (br s, 1H), 3.68 (d,  $J = 6.4$  Hz, 1H), 3.60 (br s, 1H), 3.48 (dd,  $J = 9.5, 2.0$  Hz, 1H), 3.25 (app t,  $J = 8.1$  Hz, 1H), 3.12 (app t,  $J = 13.4$  Hz, 1H), 2.66 (app dt,  $J = 6.6, 6.6$  Hz, 1H), 2.44 (dd,  $J = 14.2, 2.2$  Hz, 1H), 2.21 (dd,  $J = 13.2, 9.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  175.5, 170.8, 155.9, 138.7, 138.6, 138.3, 128.9, 128.6, 128.5, 128.1, 127.8, 127.6,

127.5, 123.2, 119.9, 108.9, 73.5, 70.9, 66.6, 65.2, 57.1, 55.5, 54.6, 52.4, 49.7, 41.2, 34.5, 32.4; IR (Neat Film, NaCl) 2950, 1735, 1654, 1474, 1437, 1265, 1208, 1099, 1069  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$ : 527.2540, found 527.2543;  $[\alpha]_{\text{D}}^{24} -85.60^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).



***N*-Methyl amine 21.** A flame-dried 1 dram vial equipped with a stir bar and a septum-bearing screw cap was charged with moist 20% w/w  $\text{Pd}(\text{OH})_2$  on carbon ( $\leq 50\%$  water) (0.062 g, 0.044 mmol) followed by a solution of lactam **20** (0.0435 g, 0.083 mmol) in MeOH (0.85 mL). The vial was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 20 h, at which point a 37% w/w aqueous solution of formaldehyde (0.310 mL, 4.14 mmol) was added via syringe. The reaction was maintained at 23 °C under hydrogen for an additional 20 h, and then filtered through a plug of Celite eluting with 10:90 MeOH/ $\text{CH}_2\text{Cl}_2$ . The solvent was removed under reduced pressure and the residue was purified via flash chromatography over silica ( $\text{CH}_2\text{Cl}_2 \rightarrow 2:98$  MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford *N*-methyl amine **21** (0.024 g, 80% yield) as a solid white foam.  $R_f = 0.28$  (10:90 MeOH/ $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (t,  $J = 7.8$  Hz, 1H), 6.81 (d,  $J = 8.3$  Hz, 1H), 6.78 (d,  $J = 7.6$  Hz, 1H), 5.72 (dd,  $J = 5.6, 3.2$  Hz, 1H), 3.91 (ddd,  $J = 11.3, 6.2, 2.9$  Hz, 1H), 3.84 (s, 3H), 3.83 (app dt,  $J = 12.4, 2.4$  Hz, 1H), 3.76 (s, 3H), 3.66 (dd,  $J = 1.5, 1.2$  Hz, 1H), 3.60 (d,  $J = 6.4$  Hz, 1H), 3.55 (ddd,  $J = 11.0, 5.6, 3.4$  Hz, 1H), 3.31 (dd,  $J = 9.5, 6.6$  Hz, 1H), 3.03 (dd,  $J = 5.6, 4.6$  Hz, 1H), 2.96 (dd,  $J = 14.6, 12.7$  Hz, 1H), 2.66 (app dt,  $J = 13.2, 6.6$  Hz, 1H), 2.62 (dd,  $J = 14.6, 2.2$  Hz, 1H), 2.48 (s, 3H), 2.39 (dd,  $J = 13.2, 9.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.9, 173.5, 156.1, 137.5, 128.8, 121.8, 120.1, 109.3, 67.4, 67.3, 66.4, 55.7, 55.4, 52.7, 52.0, 41.6, 37.3, 34.8, 32.2; IR (Neat Film,

NaCl) 3404, 2951, 1733, 1638, 1474, 1436, 1264, 1204, 1064, 915  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_5$   $[\text{M}]^+$ : 360.1685, found 360.1701;  $[\alpha]_{\text{D}}^{22} -104.64^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ).



**Quinocarcin (1).**<sup>6</sup> A flame-dried 15 mL round-bottomed flask equipped with a stir bar was charged with *N*-methyl amine **21** (36.4 mg, 0.101 mmol) in THF (2.7 mL). A solution of  $\text{LiOH} \cdot \text{H}_2\text{O}$  (0.0423 g, 1.01 mmol) in  $\text{H}_2\text{O}$  (1.35 mL) was added via syringe and the mixture was vigorously stirred at 23  $^\circ\text{C}$  for 3 h. Ethyl acetate (4 mL) was added and the solution was neutralized to pH 7 with 2.0 N HCl (4 drops). The biphasic mixture was transferred to a 50 mL round-bottomed flask and the solvents were removed under reduced pressure. The resulting cloudy white residue was dried under high vacuum for 6 h, and then suspended in THF (7 mL) and cooled to  $-78^\circ\text{C}$ . Ammonia (14 mL) was condensed into the flask using a cold finger at  $-78^\circ\text{C}$  and lithium metal (0.0401 g, 5.78 mmol) was added. The mixture turned dark blue and was vigorously stirred for 2 min. The  $-78^\circ\text{C}$  cold bath was replaced with a  $-30^\circ\text{C}$  cold bath ( $\text{MeCN}/\text{CO}_2$ ) and stirring was continued for 15 min. The reaction was quenched by the addition of methanol (5 mL) down the side of the cold finger and stirred for an additional 5 min. Solid  $\text{NH}_4\text{Cl}$  (0.960 g, 17.9 mmol) was added in portions, the cold bath was removed, and the ammonia was evaporated under a stream of argon at room temperature. Water (10 mL) was added and the mixture was neutralized to pH 7 with 1.0 N HCl (10 mL). The solvents were removed under reduced pressure, and the resulting solids were dissolved in a minimum amount of water (1 mL) and filtered through a 5 g Sep-Pak  $\text{C}_{18}$  plug ( $\text{H}_2\text{O} \rightarrow 50:50 \text{ MeOH}/\text{H}_2\text{O}$ ) to remove salts. The crude residue was purified via semi-preparative reverse-phase HPLC ( $20:80 \rightarrow 70:30 \text{ MeOH}/\text{H}_2\text{O}$ ,  $t_{\text{R}} = 33 \text{ min}$ ) to afford quinocarcin (**1**)

(0.0269 g, 81% yield over 2 steps) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.17 (t,  $J = 7.8$  Hz, 1H), 6.85 (d,  $J = 8.3$  Hz, 1H), 6.76 (d,  $J = 7.6$  Hz, 1H), 4.57 (d,  $J = 2.9$  Hz, 1H), 4.55 (dd,  $J = 7.3, 2.9$  Hz, 1H), 4.07 (br s, 2H), 3.82 (s, 3H), 3.68 (dd,  $J = 10.7, 2.9$  Hz, 1H), 3.43–3.33 (comp m, 2H), 3.39 (dd,  $J = 10.7, 7.3$  Hz, 1H), 2.79–2.74 (m, 1H), 2.77 (s, 3H), 2.64 (dd,  $J = 14.6, 2.4$  Hz, 1H), 2.64–2.60 (m, 1H), 2.46 (dd,  $J = 13.9, 10.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  179.5, 157.2, 137.6, 129.1, 124.0, 121.3, 110.0, 92.6, 73.2, 68.2, 66.9, 56.3, 55.9, 55.7, 42.8, 40.7, 32.9, 28.3; IR (Neat Film, NaCl) 3370, 2941, 1590, 1474, 1383, 1264, 1054  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 331.1652, found 331.1669;  $[\alpha]_{\text{D}}^{22} -31.57^\circ$  (c 0.28,  $\text{H}_2\text{O}$ ). The analytical data for the synthetic sample matched those for the natural sample in all respects.<sup>7</sup>

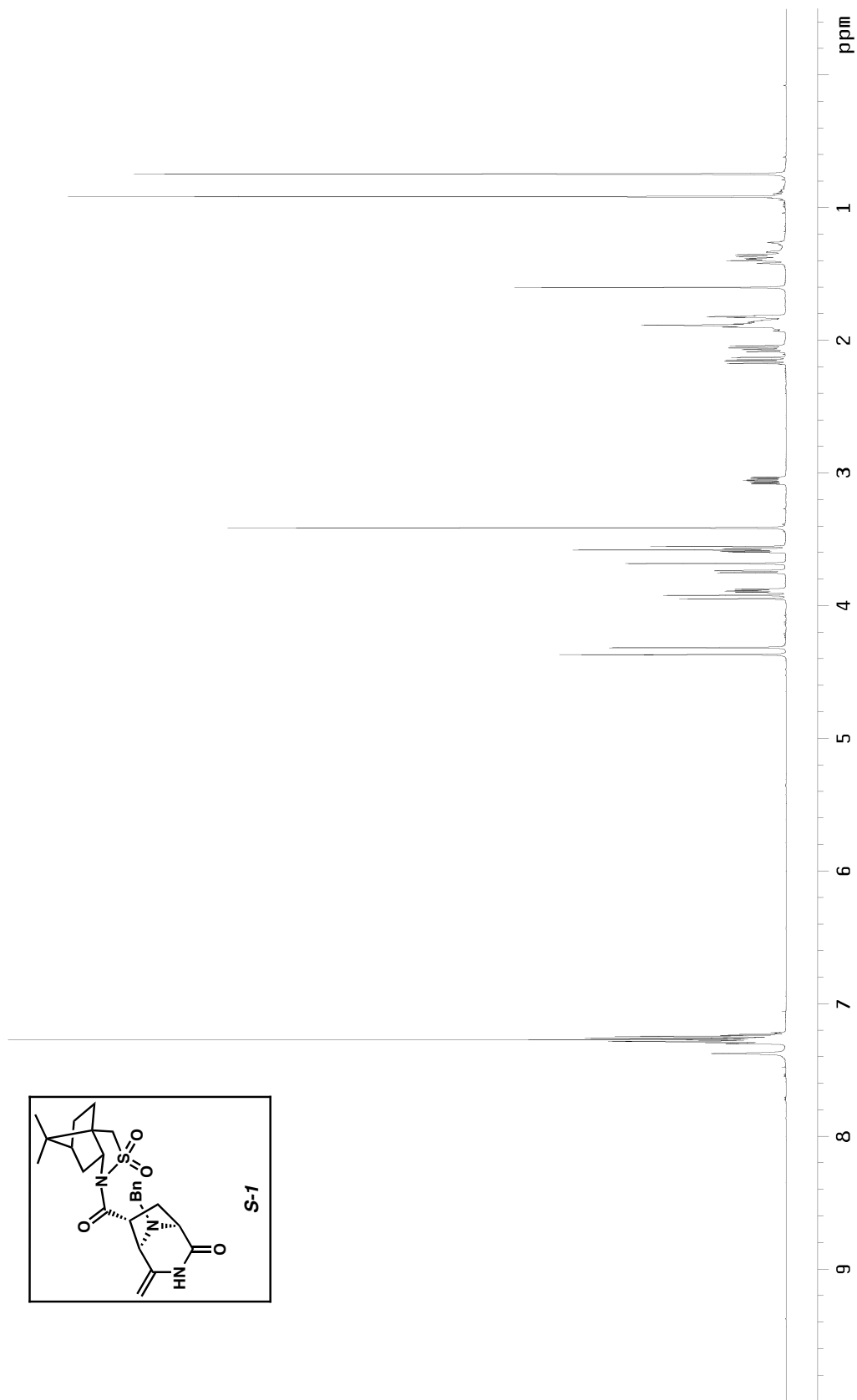
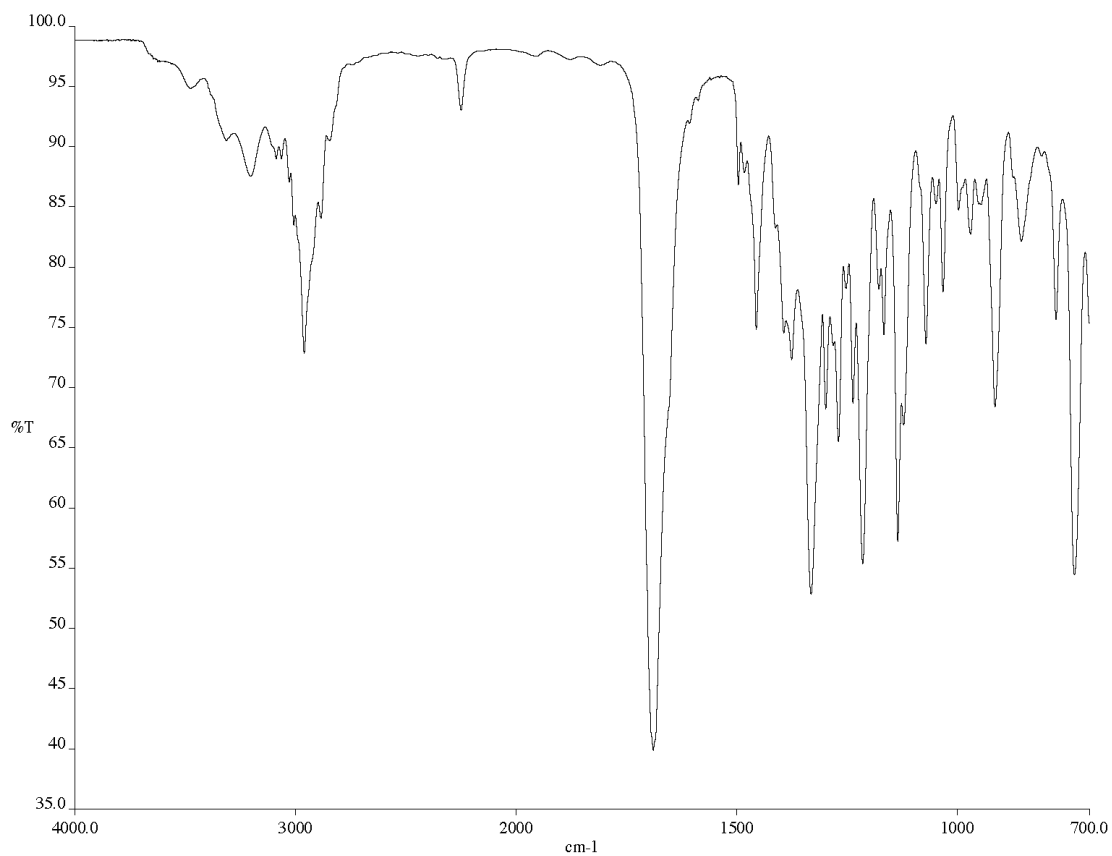
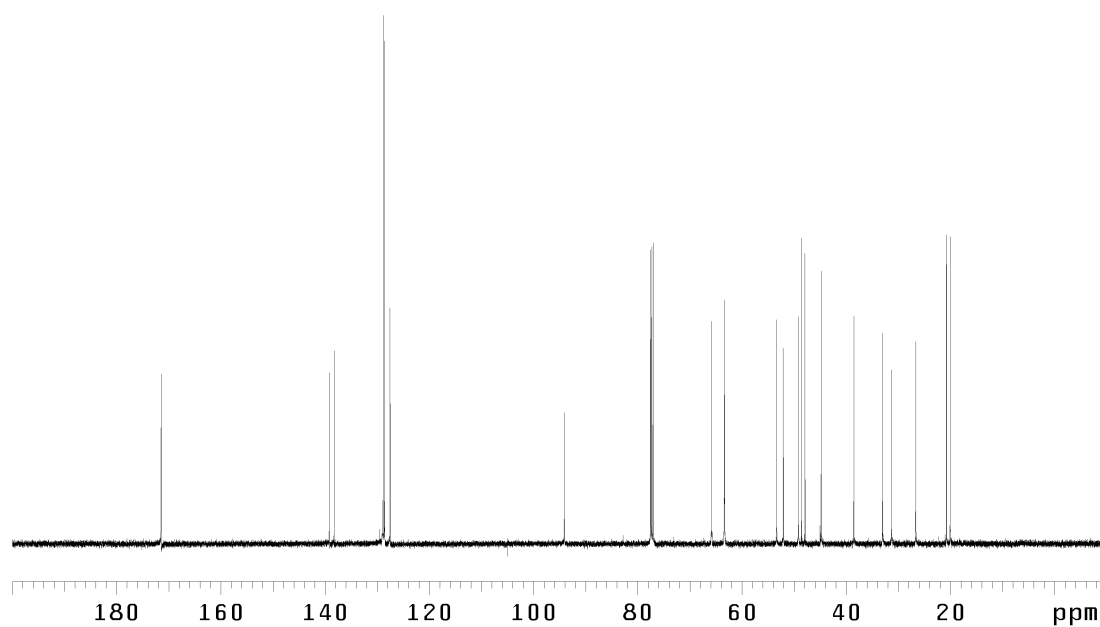


Figure 1.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of diazabicyclic **S-1**



*Figure 1.2.* Infrared spectrum (thin film/NaCl) of diazabicyclic **S-1**.



*Figure 1.3*  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of diazabicyclic **S-1**.

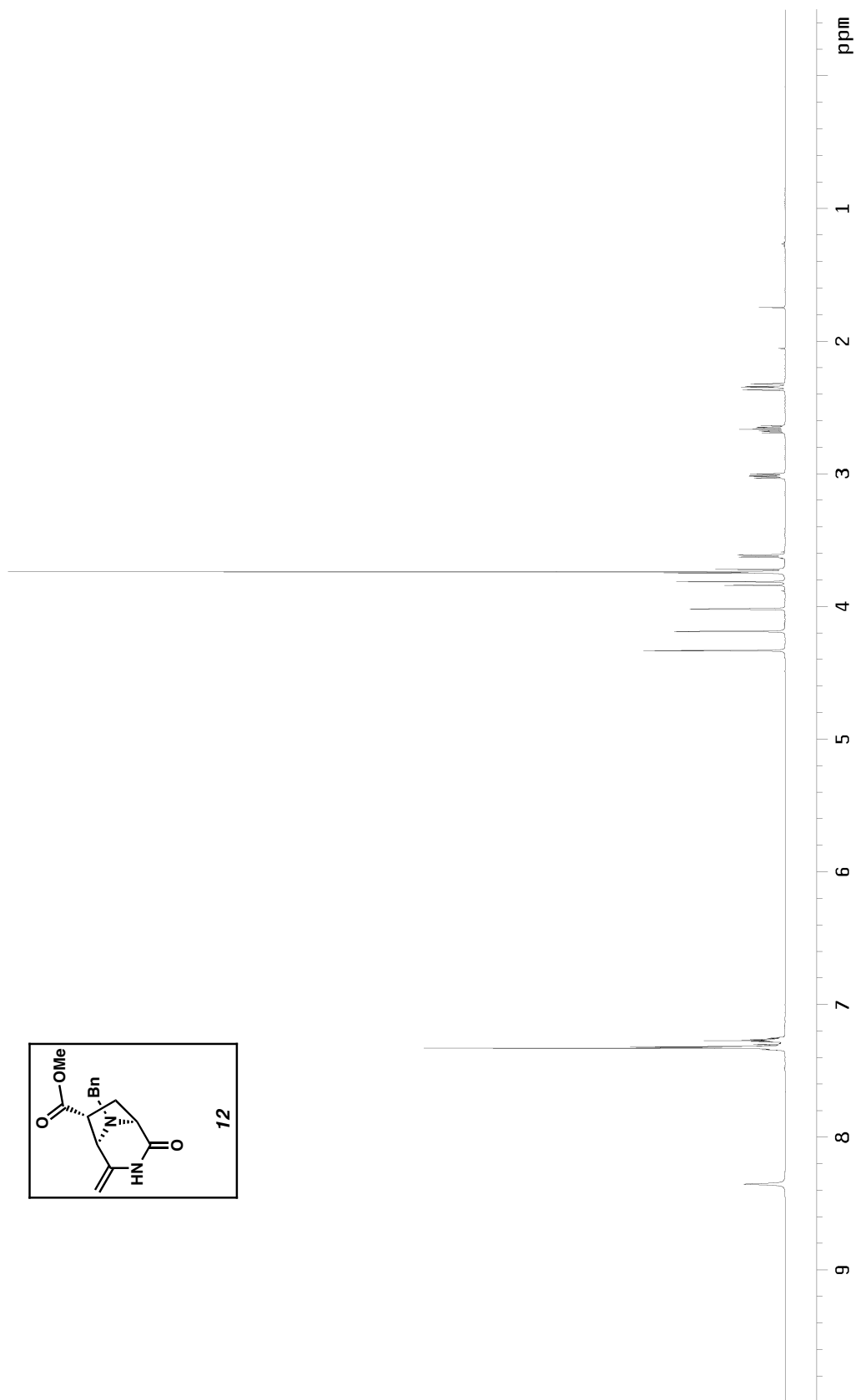
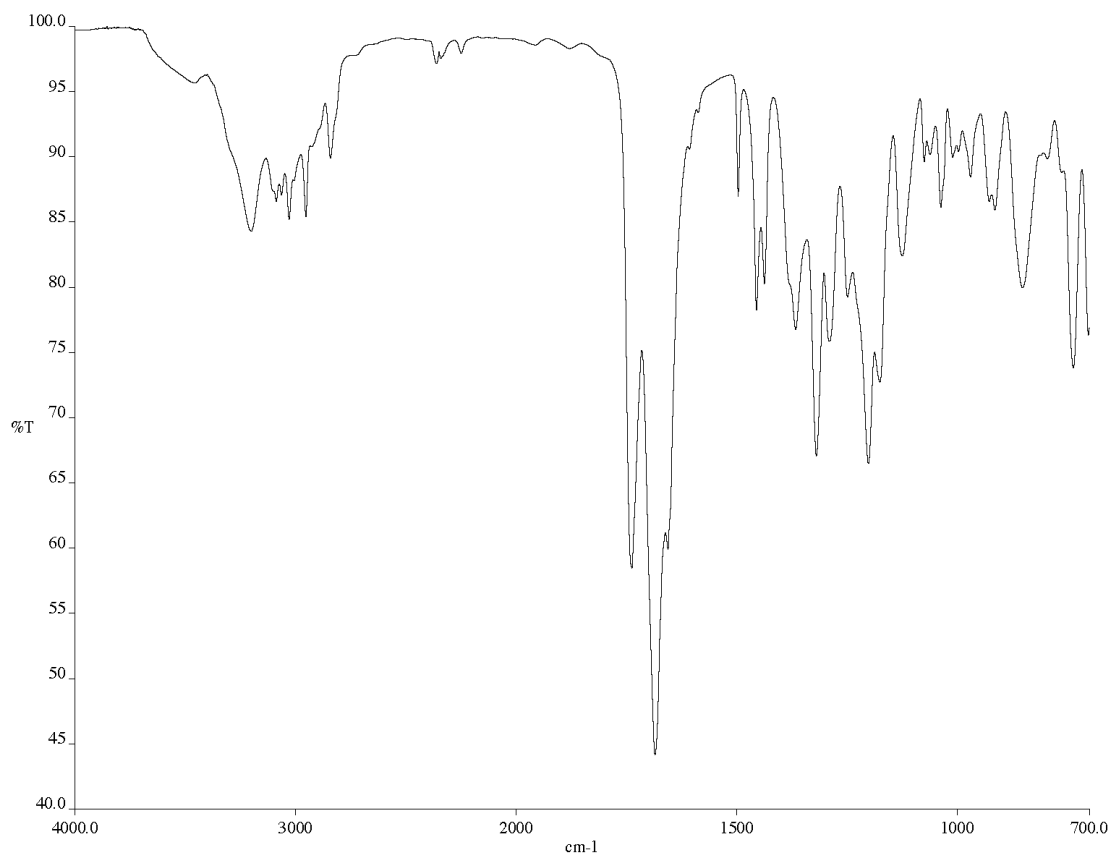
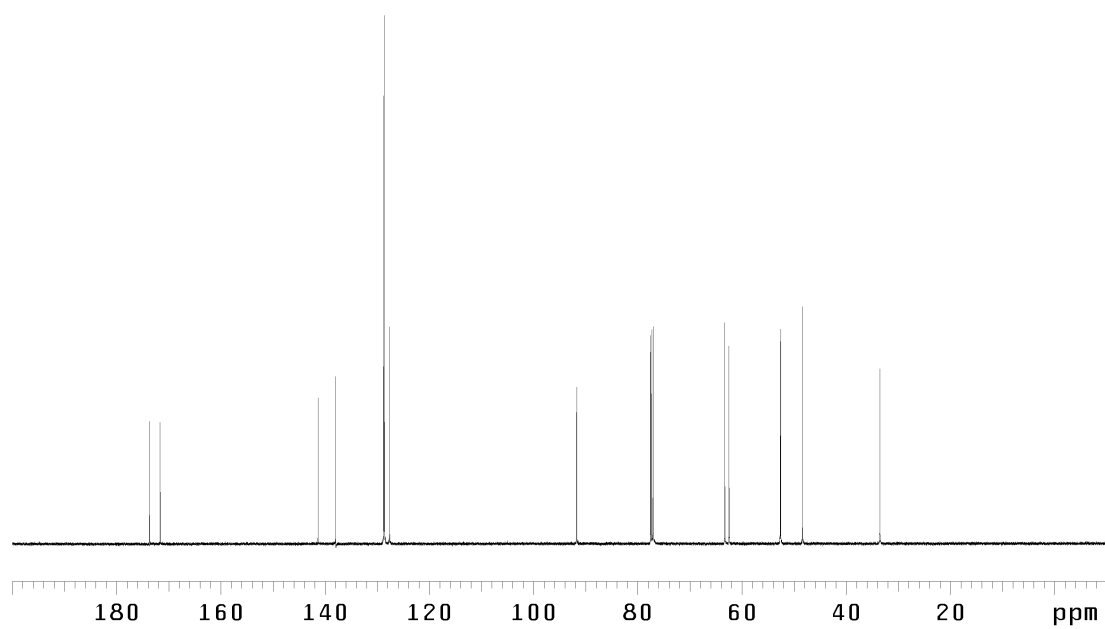


Figure 2.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of methyl ester **12**.





*Figure 2.2.* Infrared spectrum (thin film/NaCl) of methyl ester **12**.

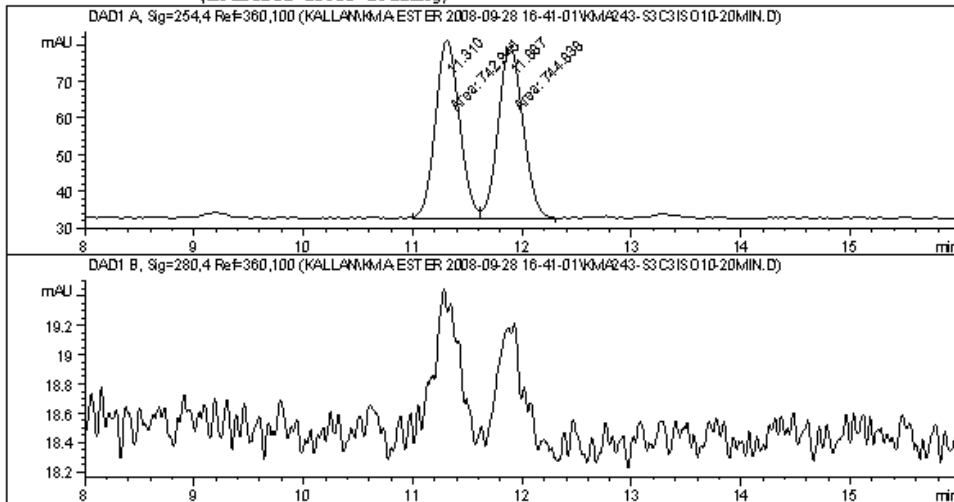


*Figure 2.3.* <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of methyl ester **12**.

Figure 2.4. Chiral SFC traces for racemic methyl ester **12**.

Data File C:\CHEM32\1\DATA\KALLAN\KMA-ESTER 2008-09-28 16-41-01\KMA243-S3C3IS010-20MIN.D  
Sample Name: kma-xiii-243.2

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Acq. Instrument : Instrument 1                 Location  : P1-D-02
Injection Date  : 9/28/2008 4:45:18 PM        Inj       :    1
                                           Inj Volume: 5 µl
Acq. Method     : C:\Chem32\1\DATA\KALLAN\KMA-ESTER 2008-09-28 16-41-01\KMA-CHIRAL S3C3
                  ISO10-20MIN-2.M
Last changed    : 9/28/2008 3:34:13 PM by JST
Analysis Method : C:\CHEM32\1\DATA\JST2\JST 2008-09-28 14-45-41\KMA243-2.D\DA.M (KMA-
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Last changed    : 9/28/2008 5:19:28 PM by SKEDROWSKI
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Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs
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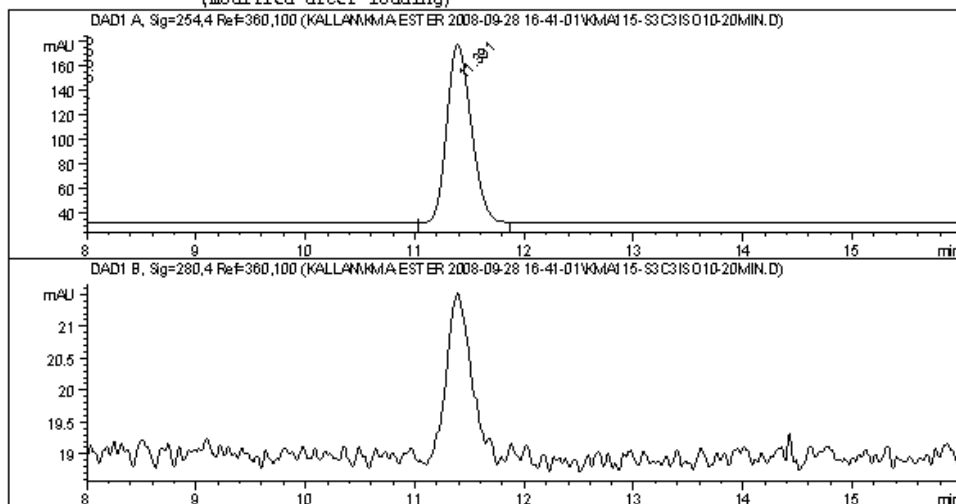
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2	11.887	MM	0.2632	744.83813	47.16733	50.0636

Totals : 1487.78345 95.85054

Figure 2.5. Chiral SFC trace for enantioenriched methyl ester (–)-**12** (>99% ee).

Data File C:\CHEM32\1\DATA\KALLAN\KMA-ESTER 2008-09-28 16-41-01\KMA115-S3C3IS010-20MIN.D  
Sample Name: kma-xiii-115.3

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                                           Inj Volume: 5 µl
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Use Multiplier & Dilution Factor with ISTDs
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Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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Totals : 2826.86035 156.79543

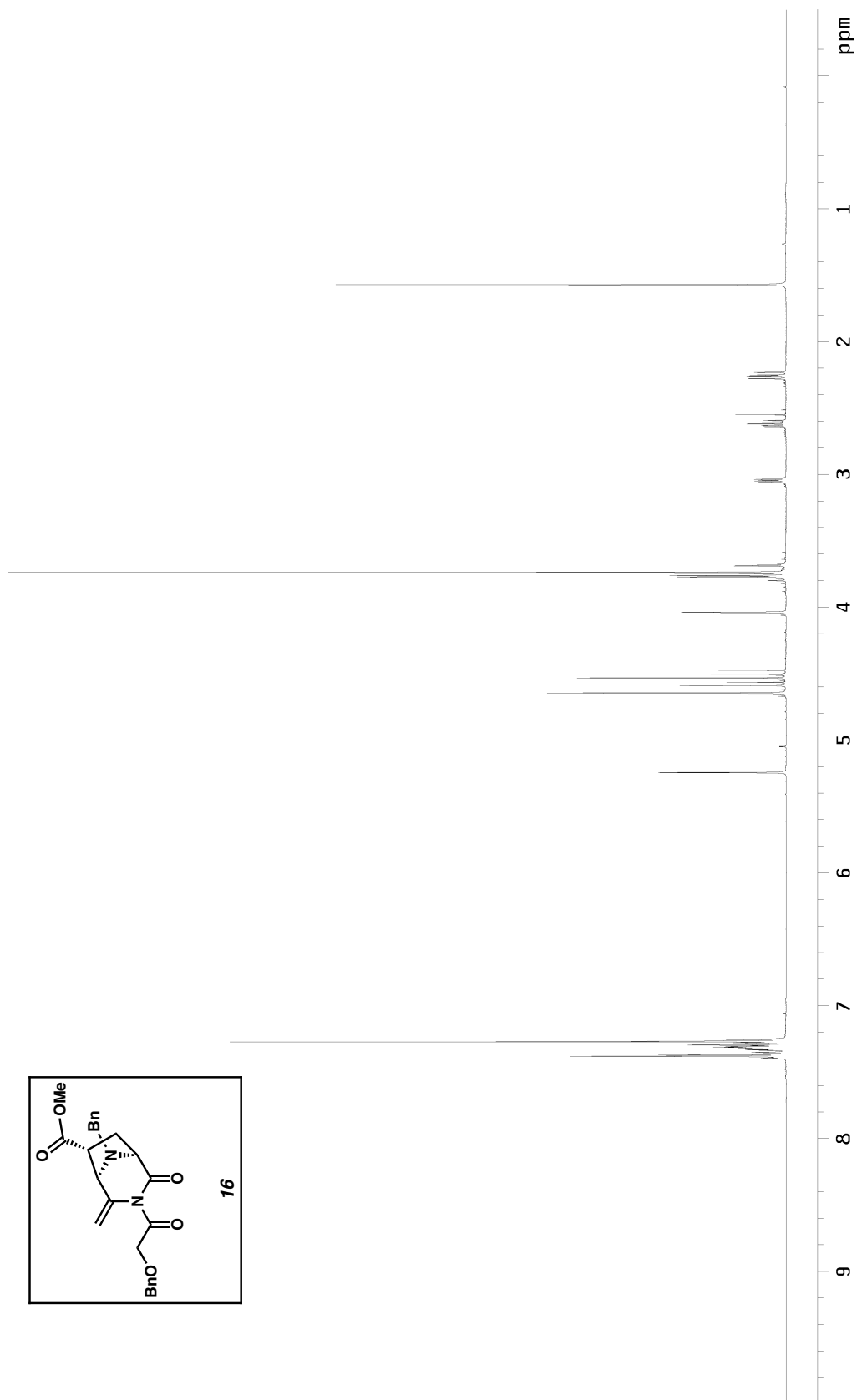
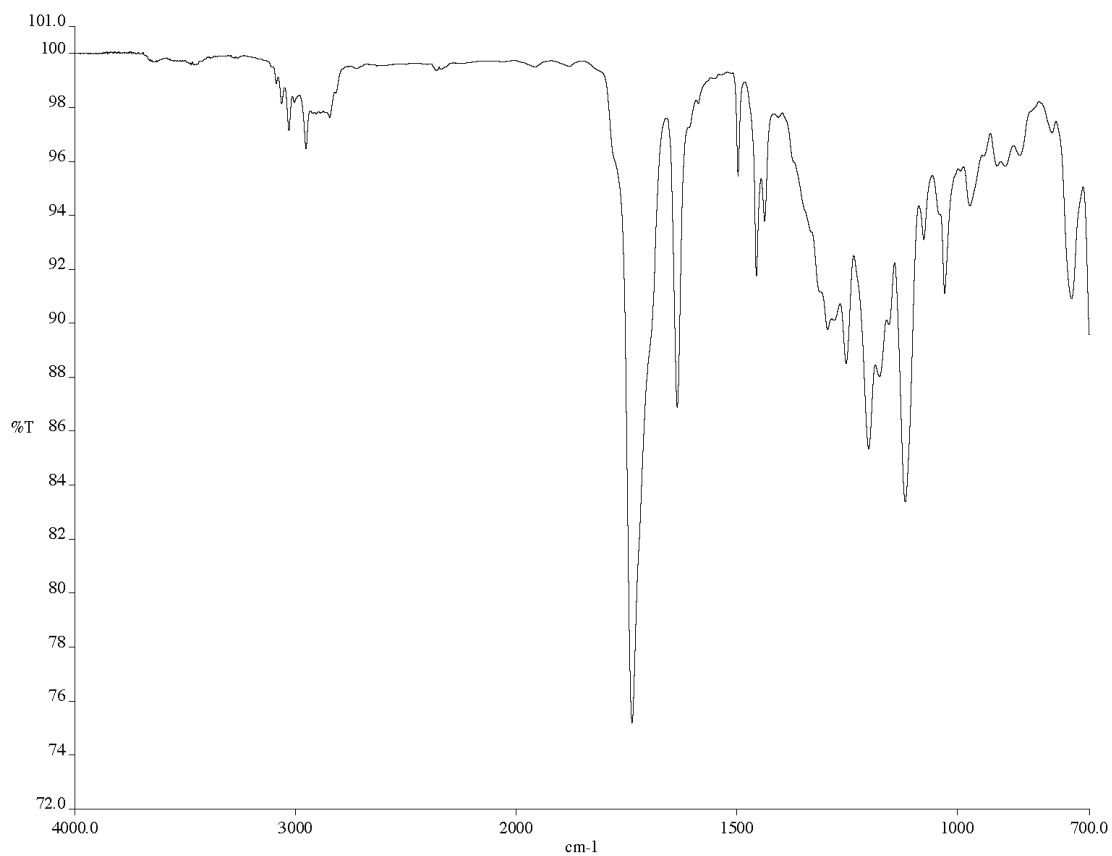
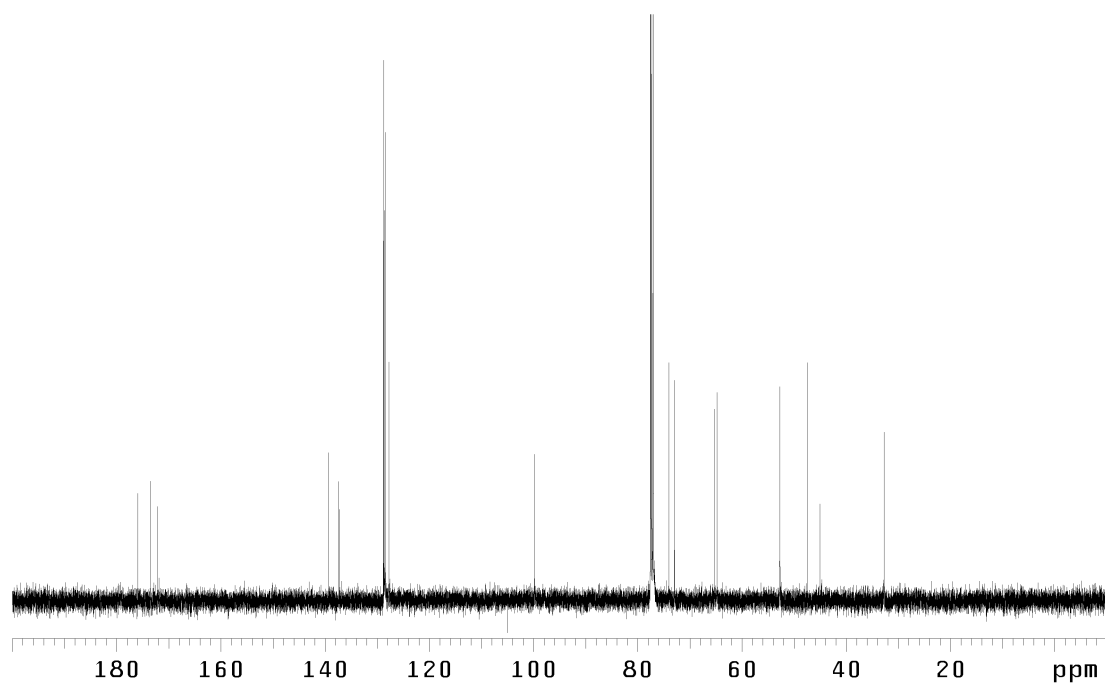


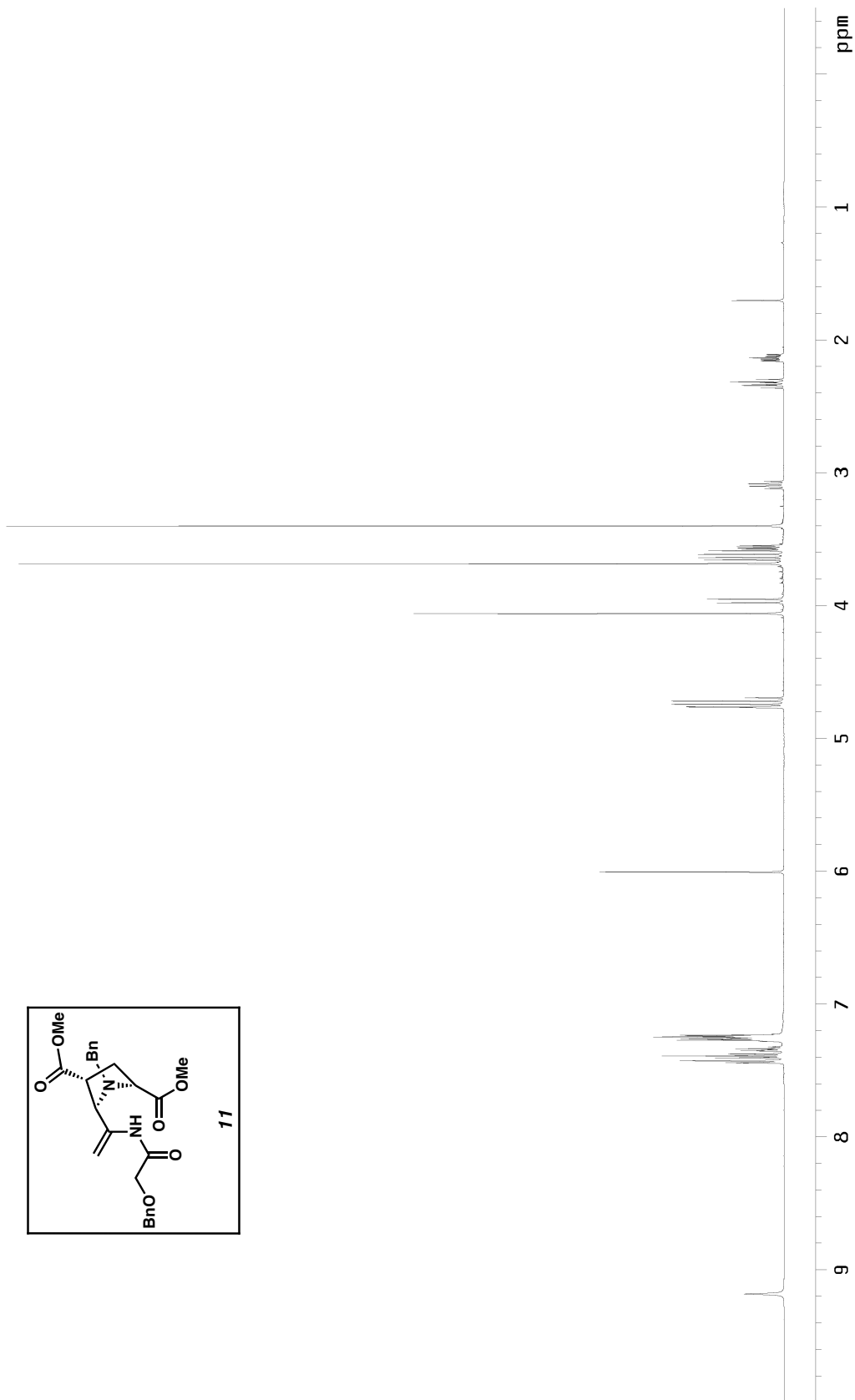
Figure 3.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of imide **16**.



*Figure 3.2.* Infrared spectrum (thin film/NaCl) of imide **16**.



*Figure 3.3.* <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of imide **16**.



**Figure 4.1.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of *N*-acyl enamine **11**.

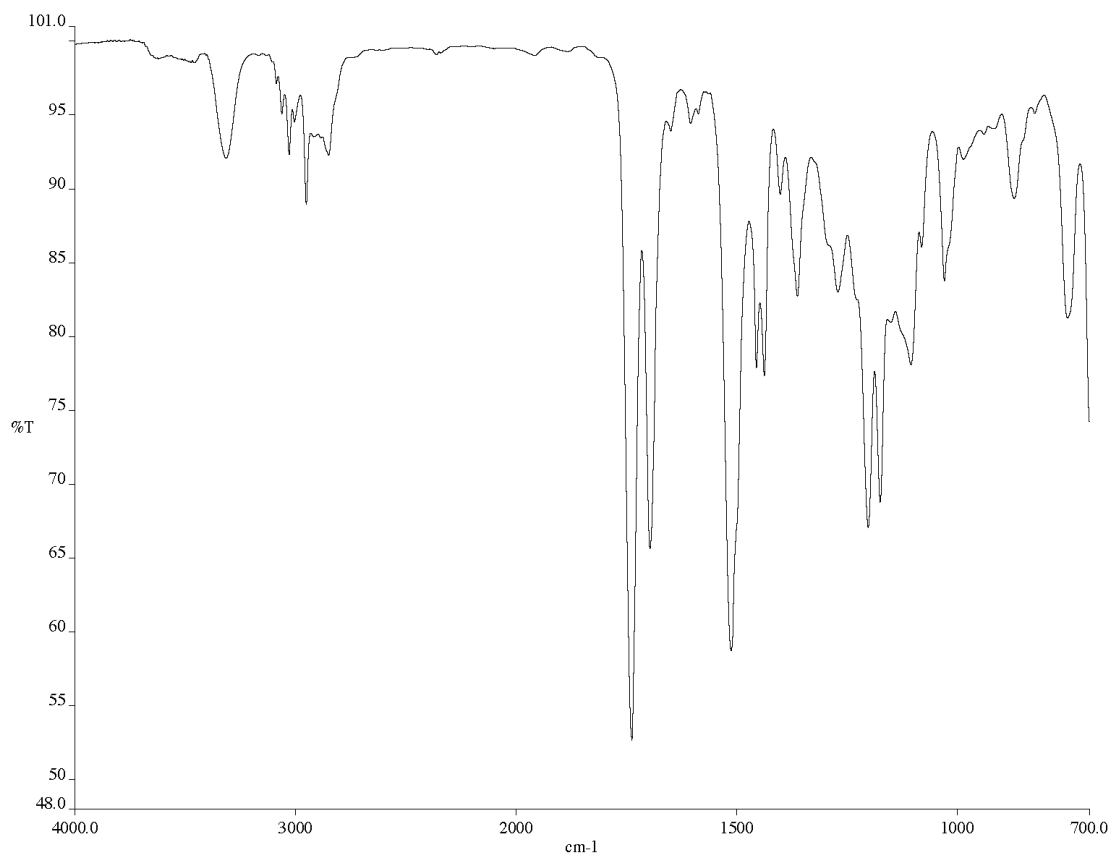


Figure 4.2. Infrared spectrum (thin film/NaCl) of *N*-acyl enamine **11**.

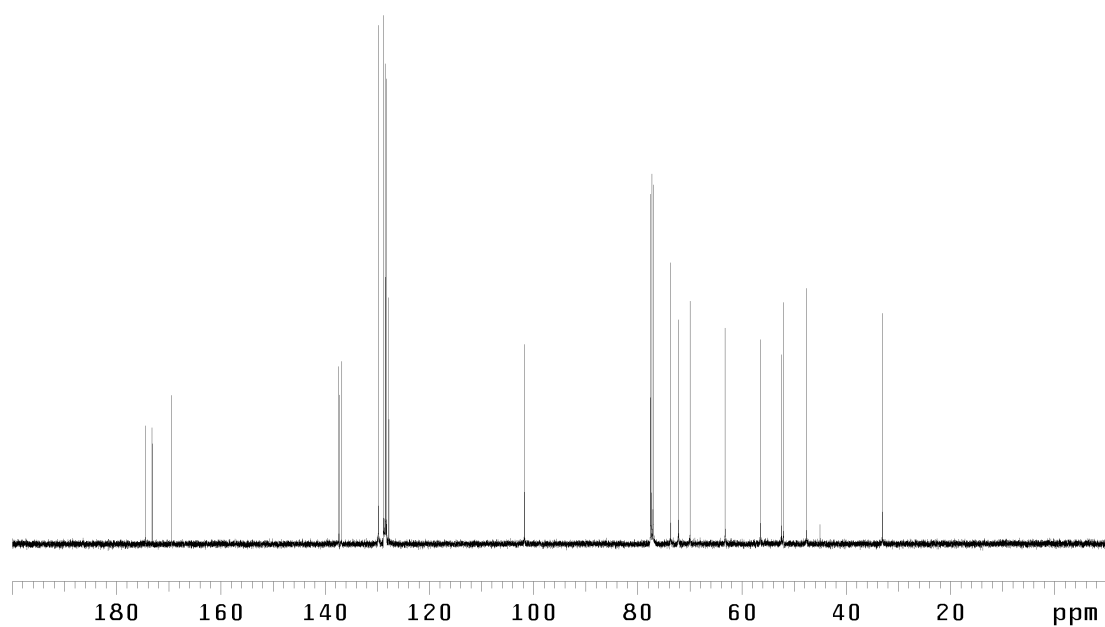


Figure 4.3. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of *N*-acyl enamine **11**.

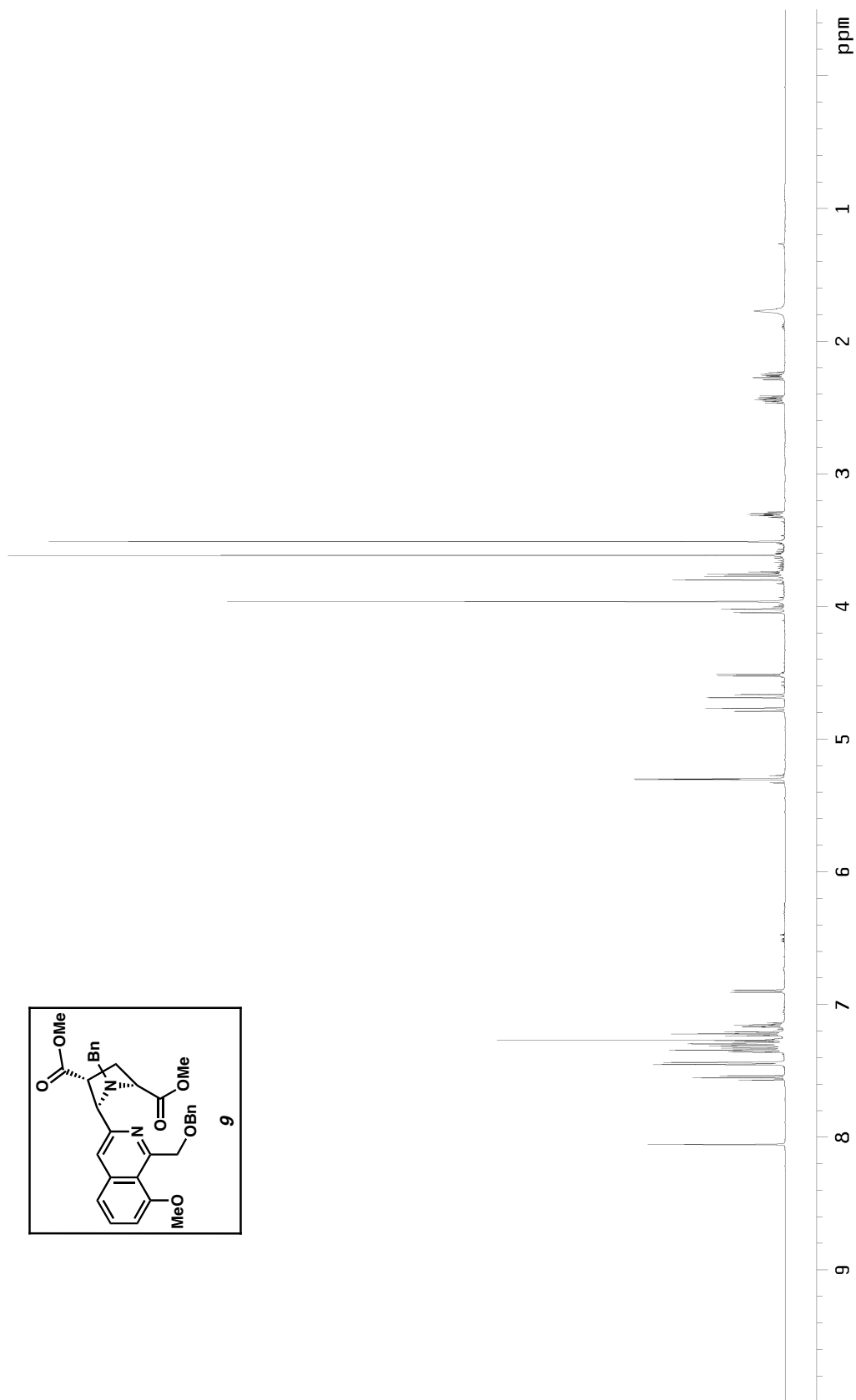


Figure 5.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of isoquinoline **9**.



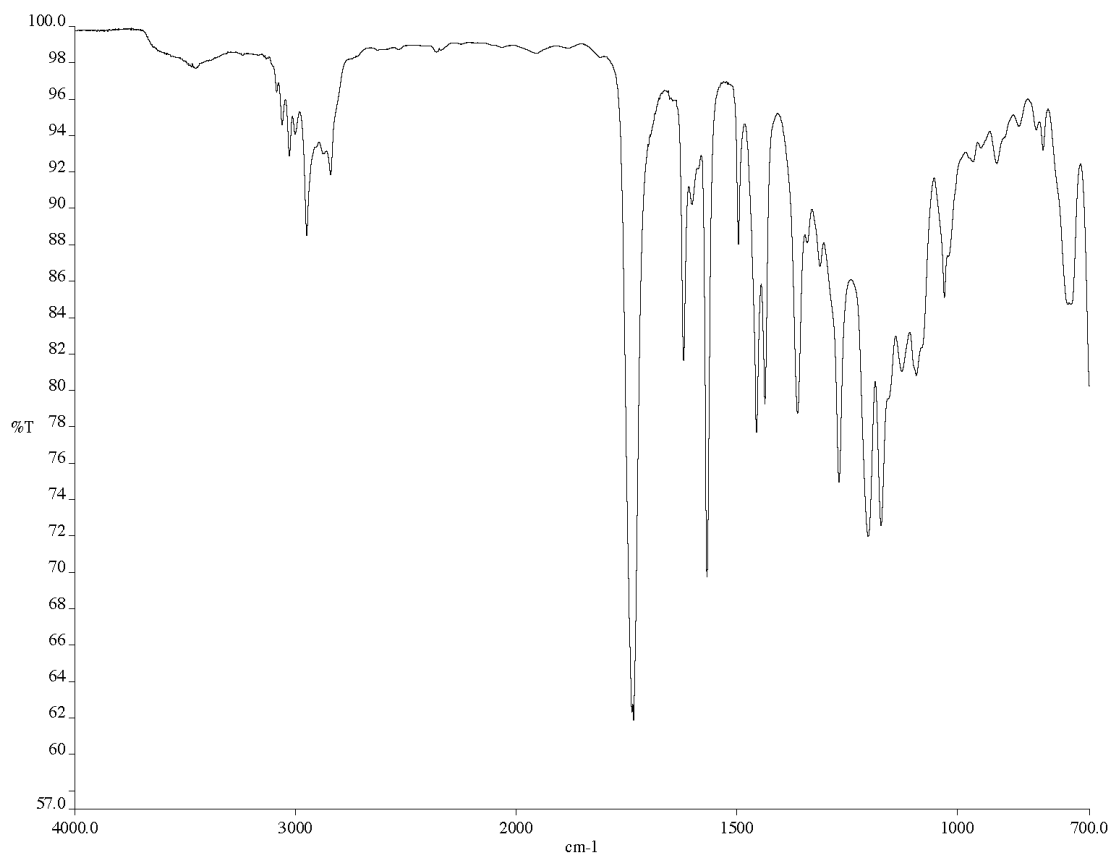


Figure 5.2. Infrared spectrum (thin film/NaCl) of isoquinoline **9**.

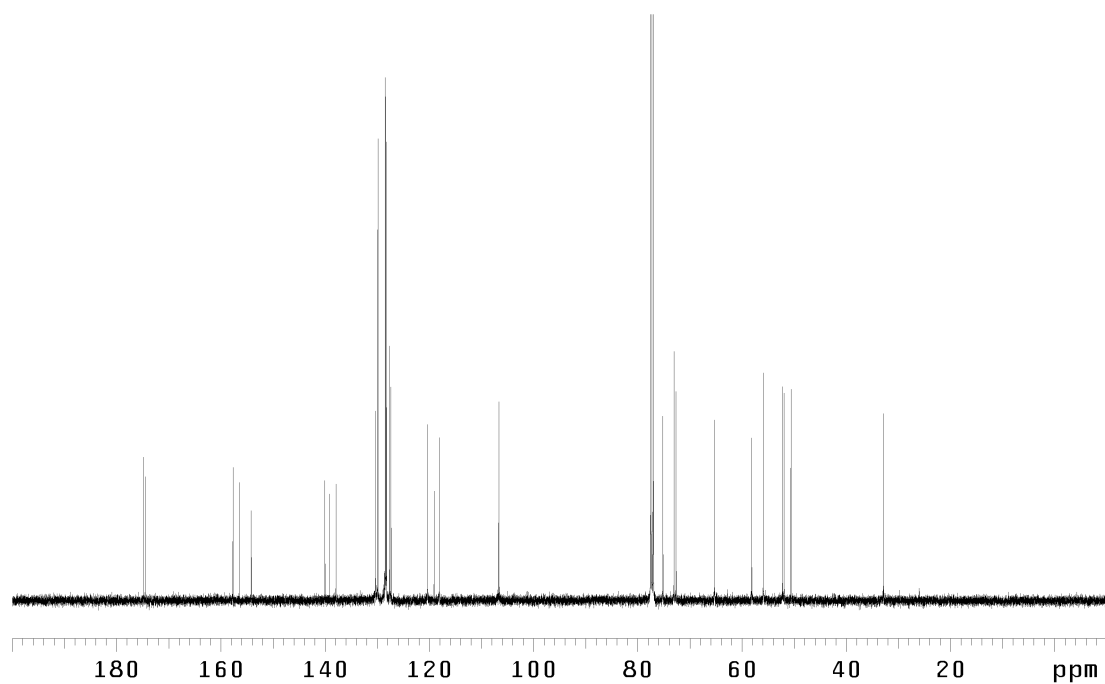


Figure 5.3. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of isoquinoline **9**.

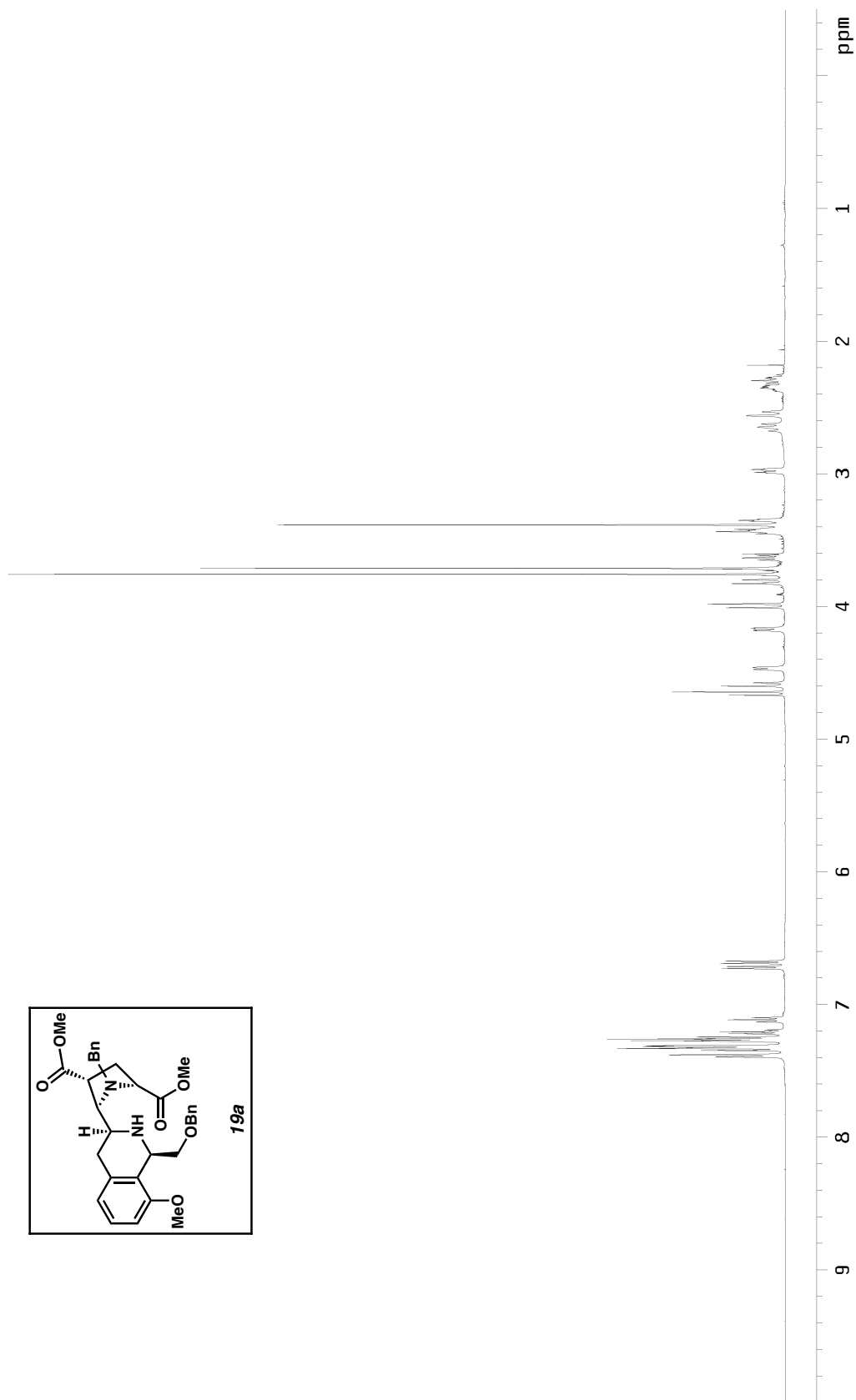


Figure 6.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of tetrahydroisoquinoline **19a**.

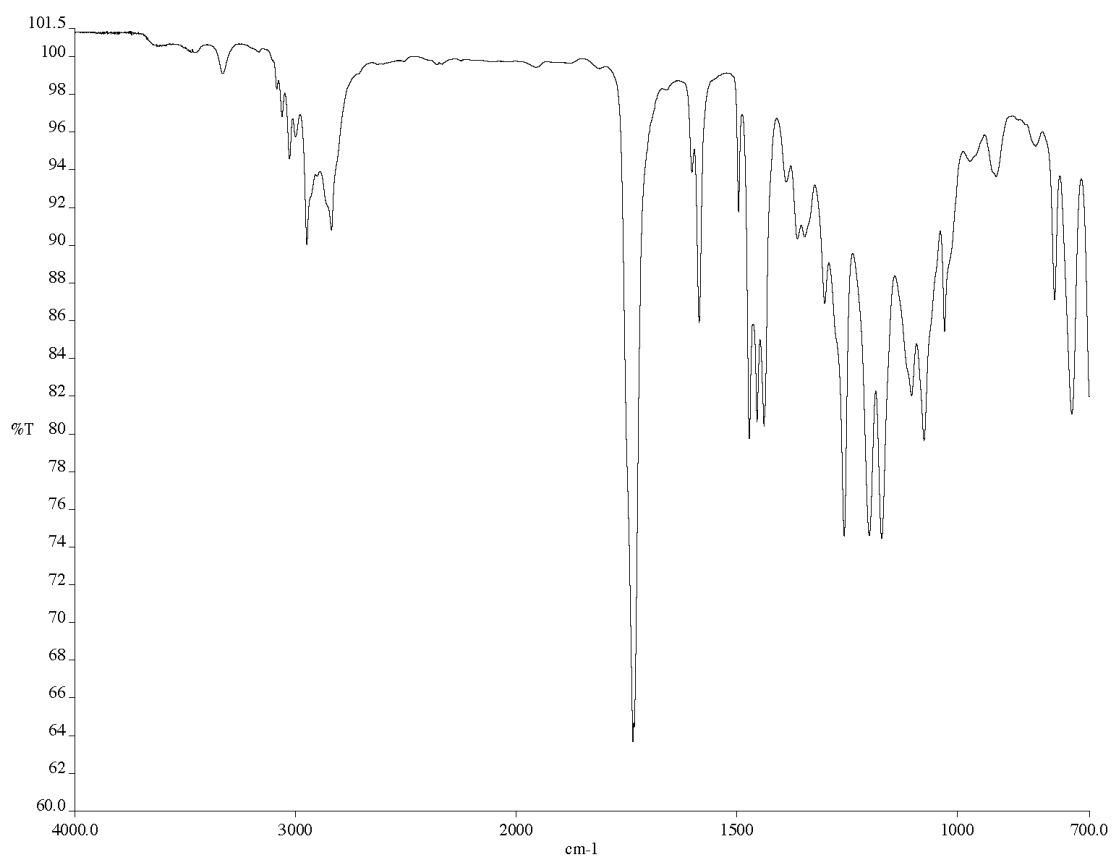


Figure 6.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline **19a**.

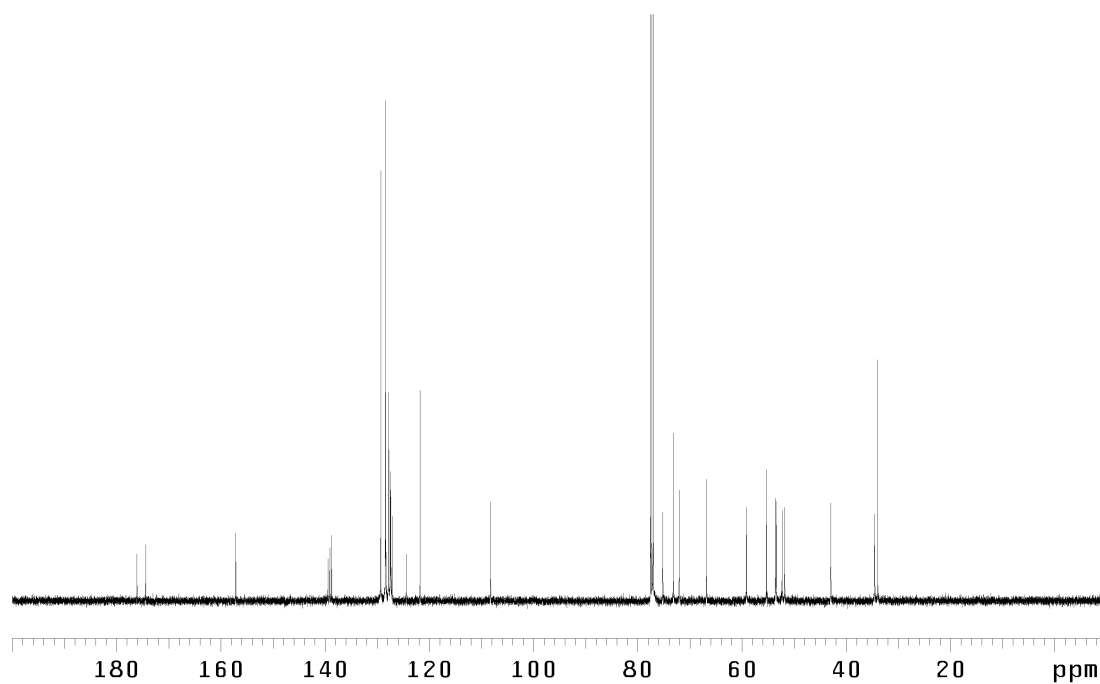


Figure 6.3. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of tetrahydroisoquinoline **19a**.

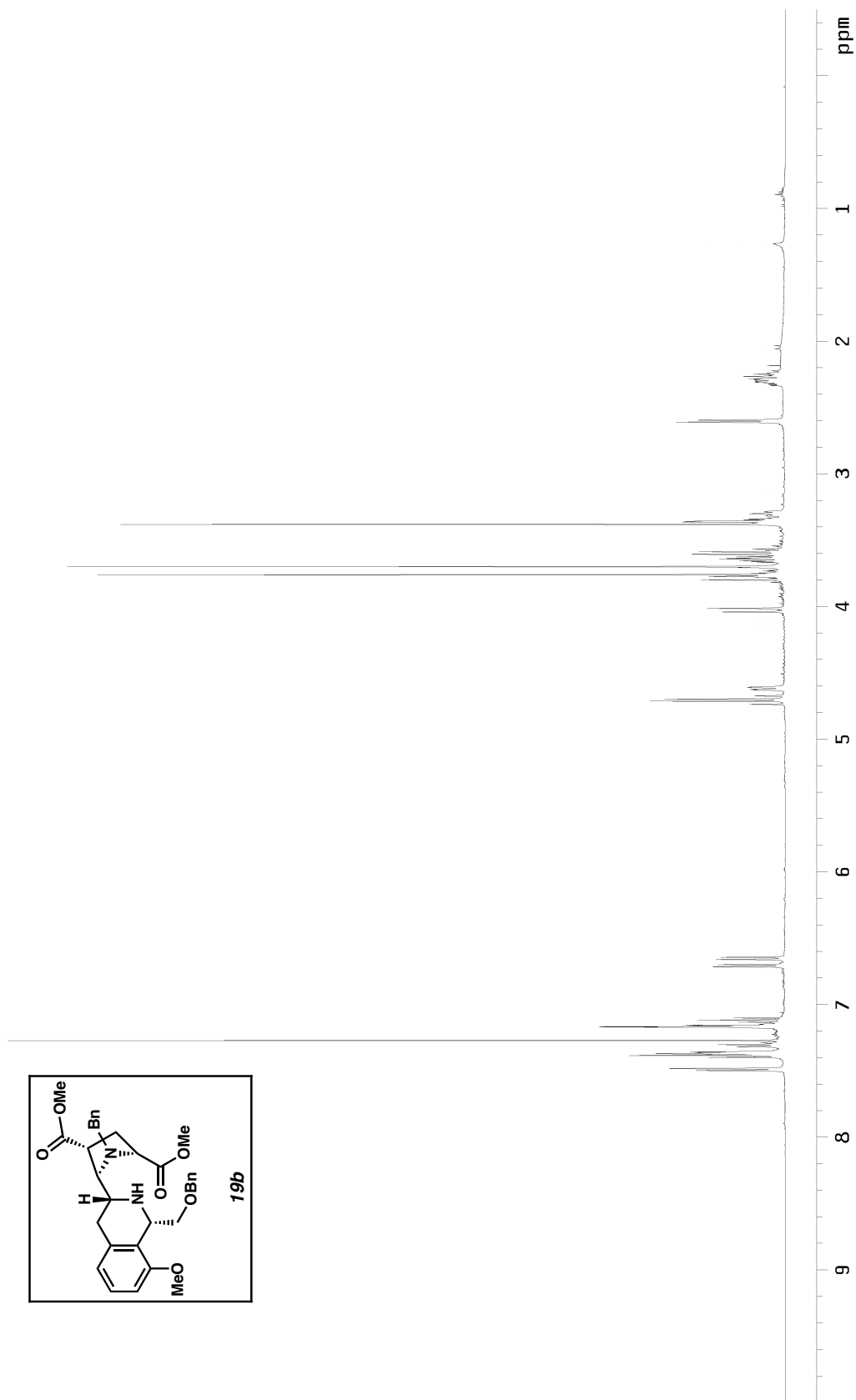


Figure 7.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of tetrahydroisoquinoline **19b**.

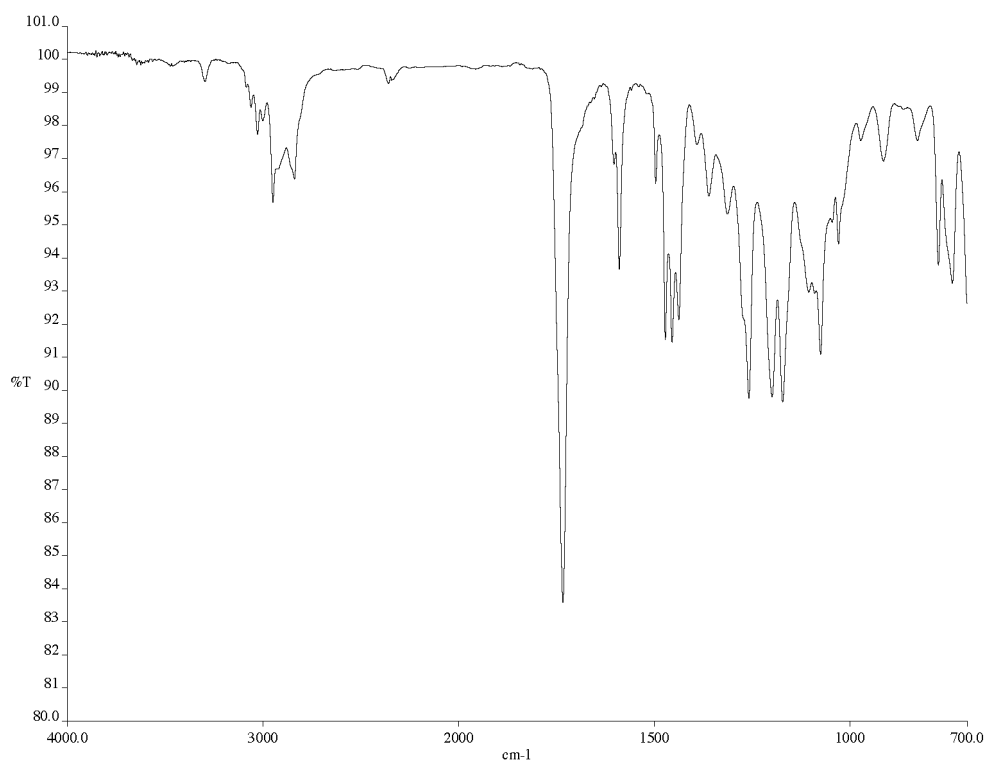


Figure 7.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline **19b**.

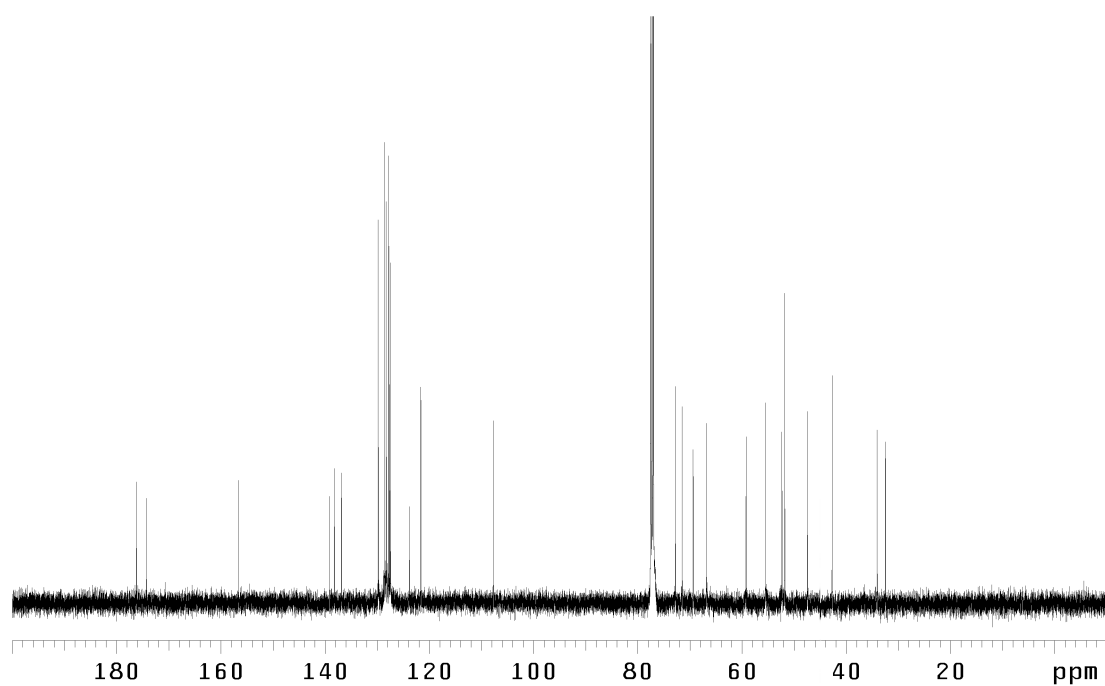


Figure 7.3.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of tetrahydroisoquinoline **19b**.

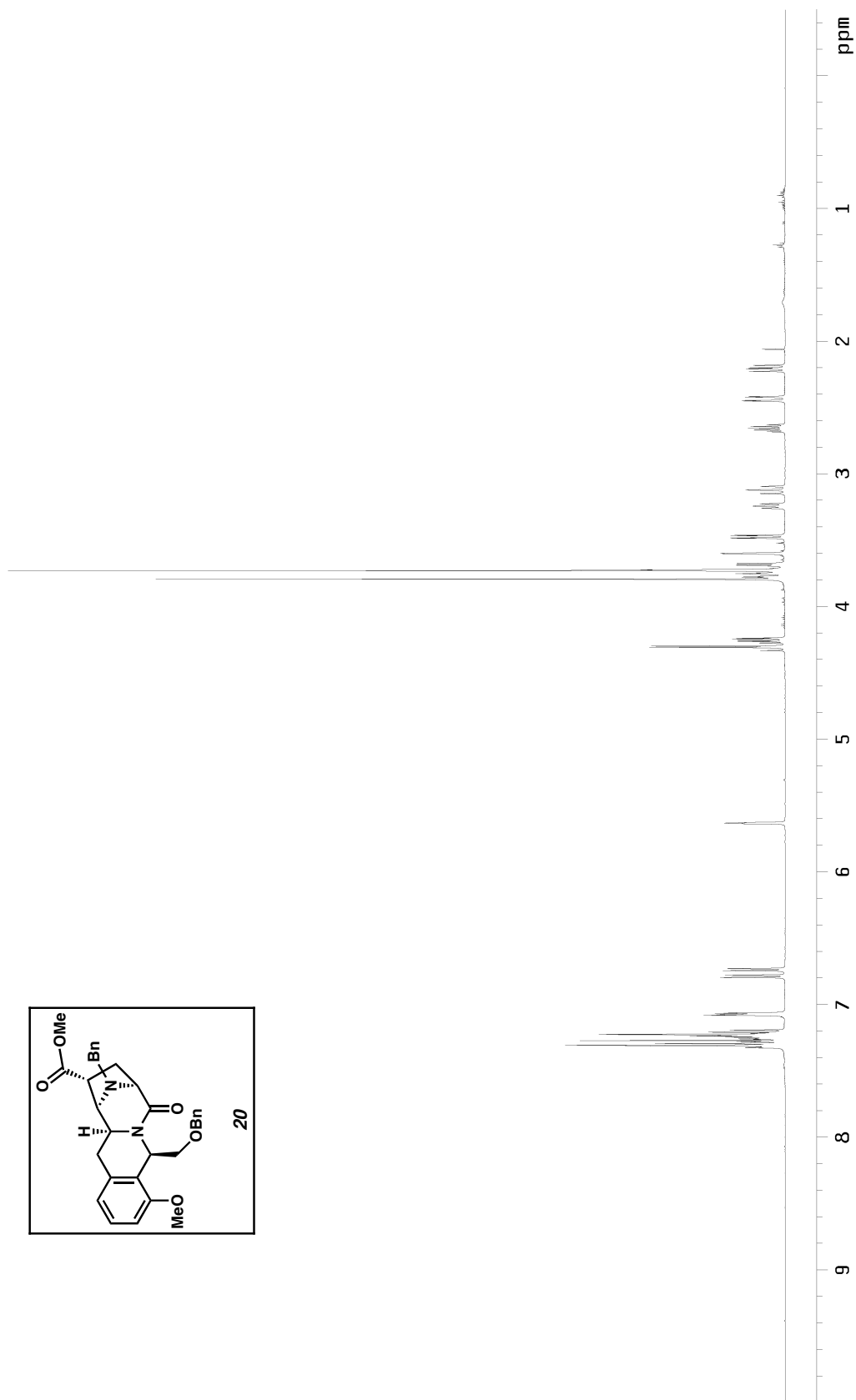
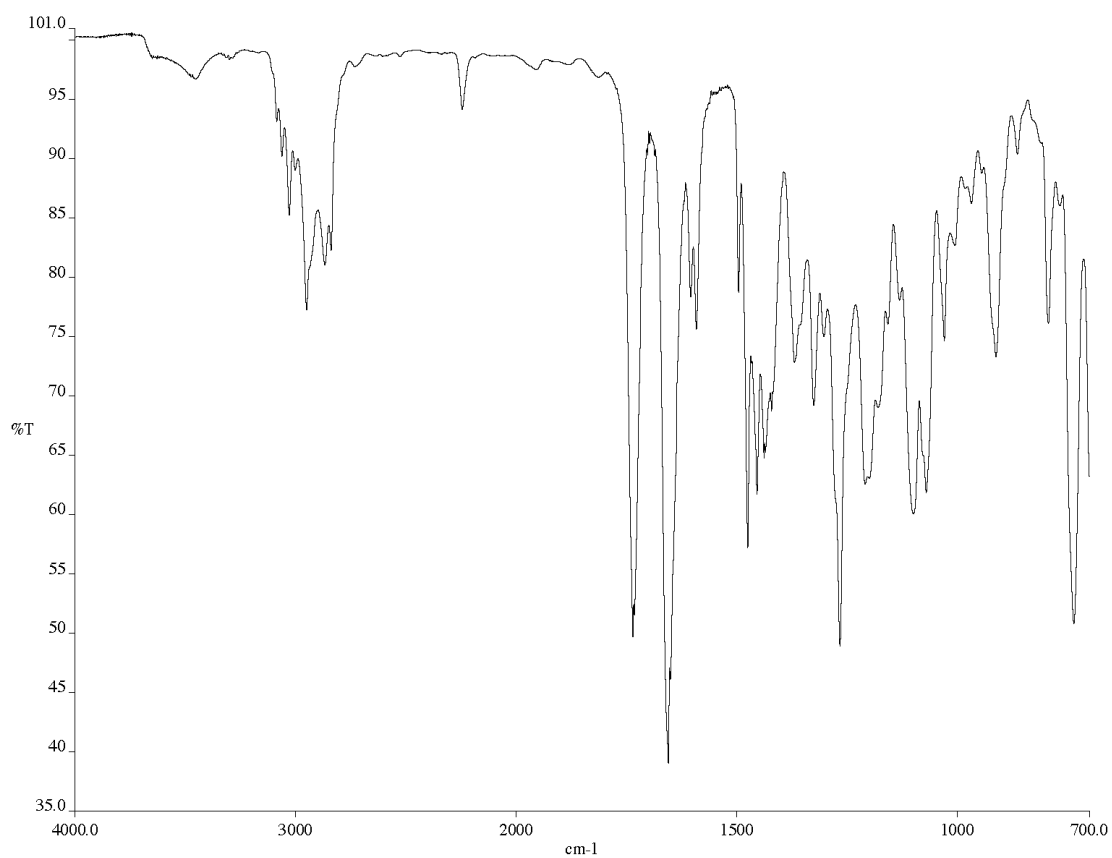
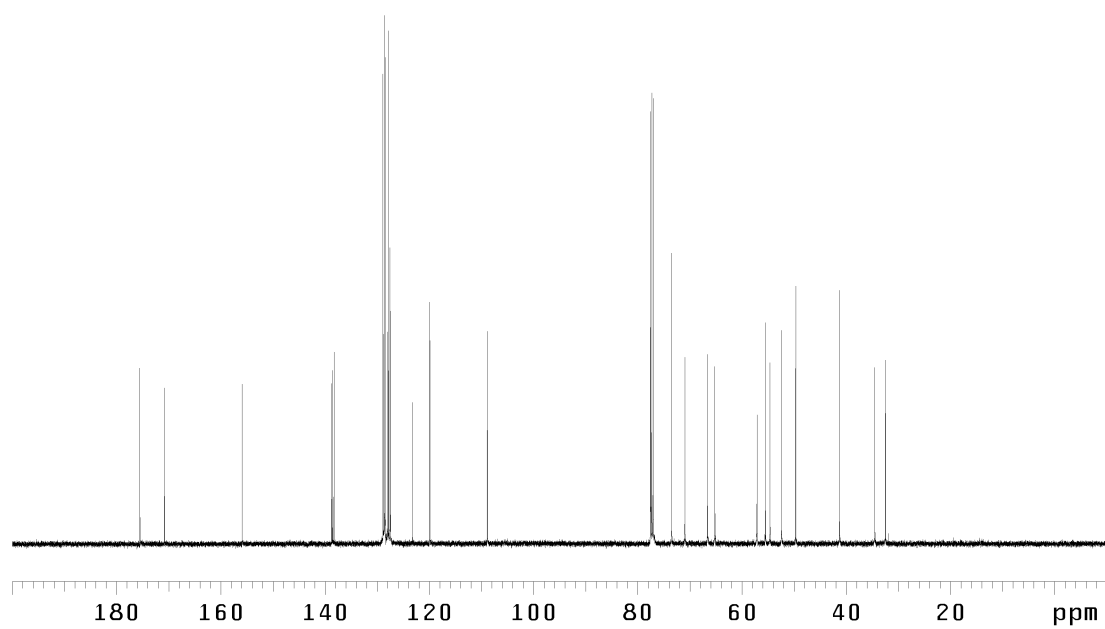


Figure 8.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of lactam **20**.



*Figure 8.2.* Infrared spectrum (thin film/NaCl) of lactam **20**.



*Figure 8.3.* <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) of lactam **20**.

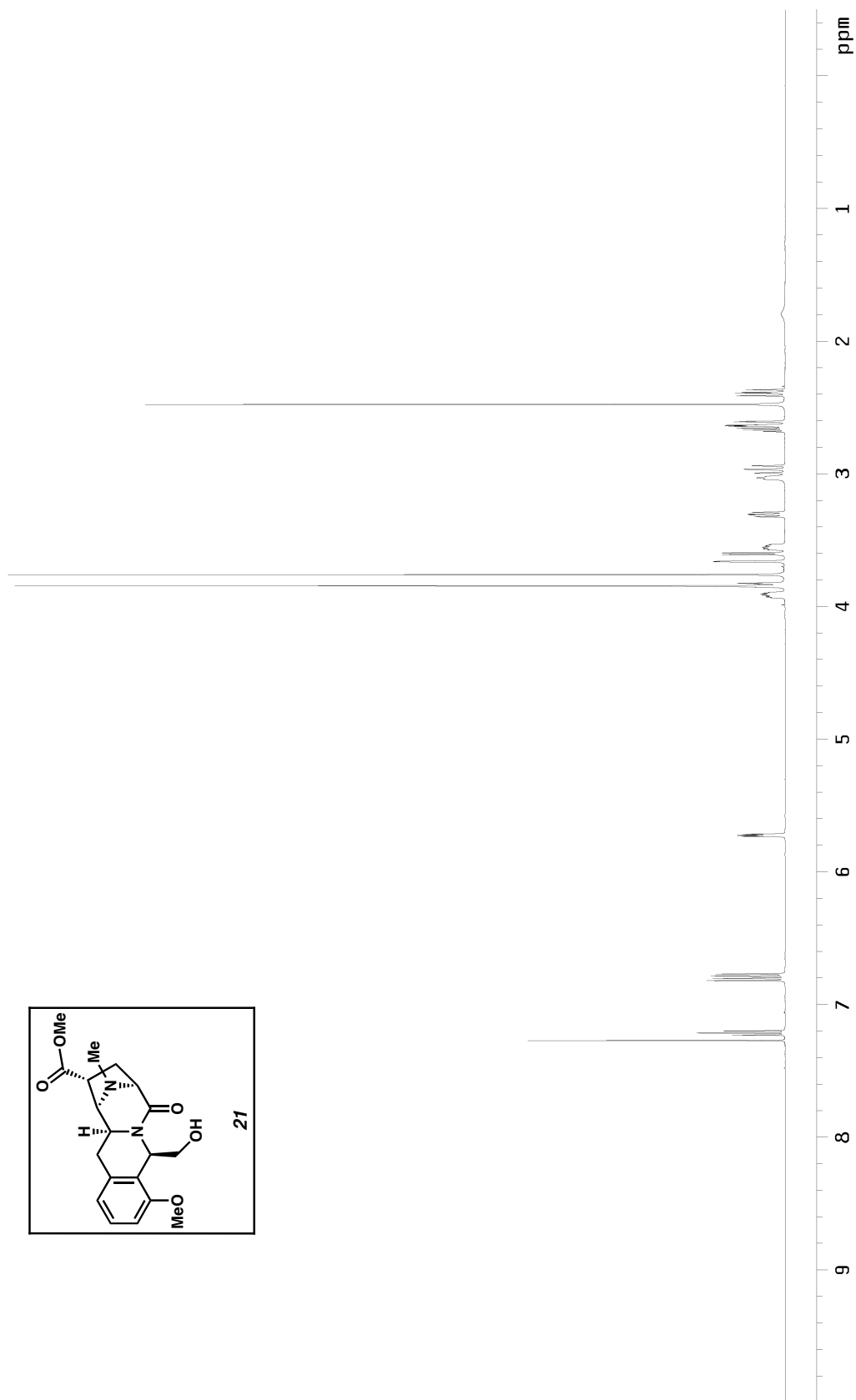


Figure 9.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of *N*-methyl amine **21**.



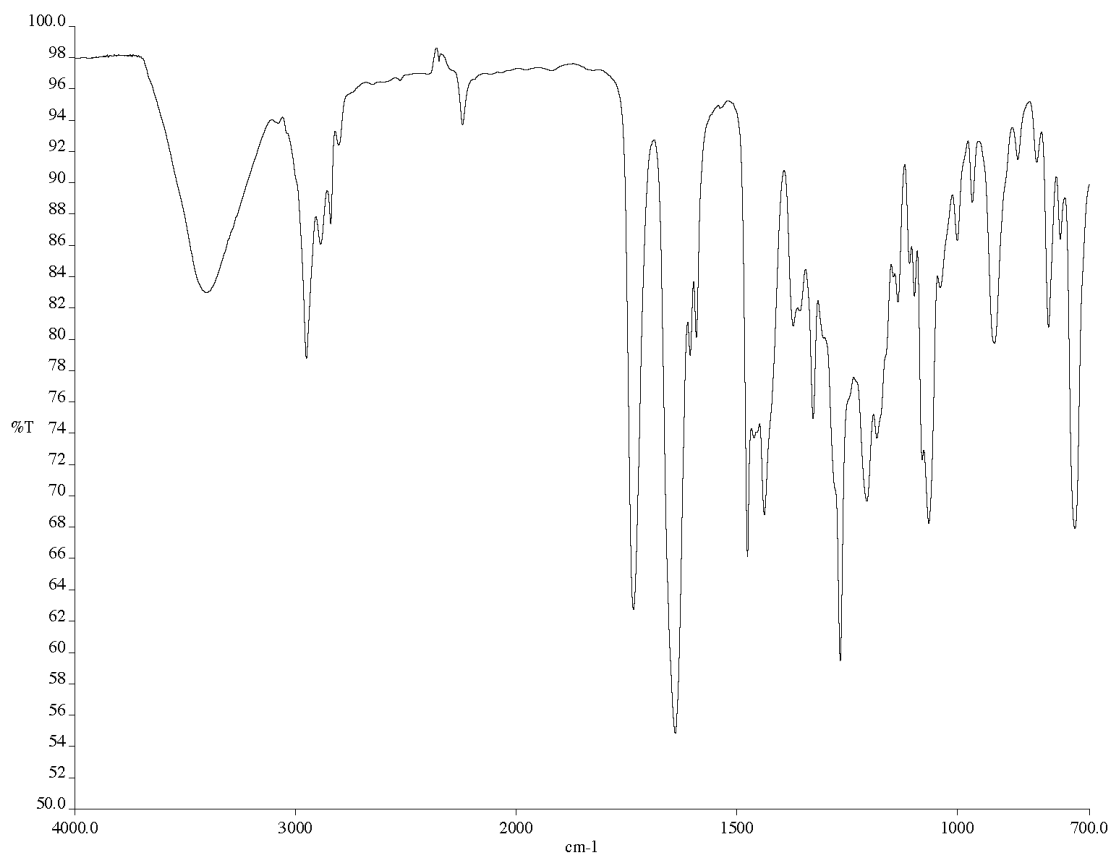


Figure 9.2. Infrared spectrum (thin film/NaCl) of *N*-methyl amine **21**.

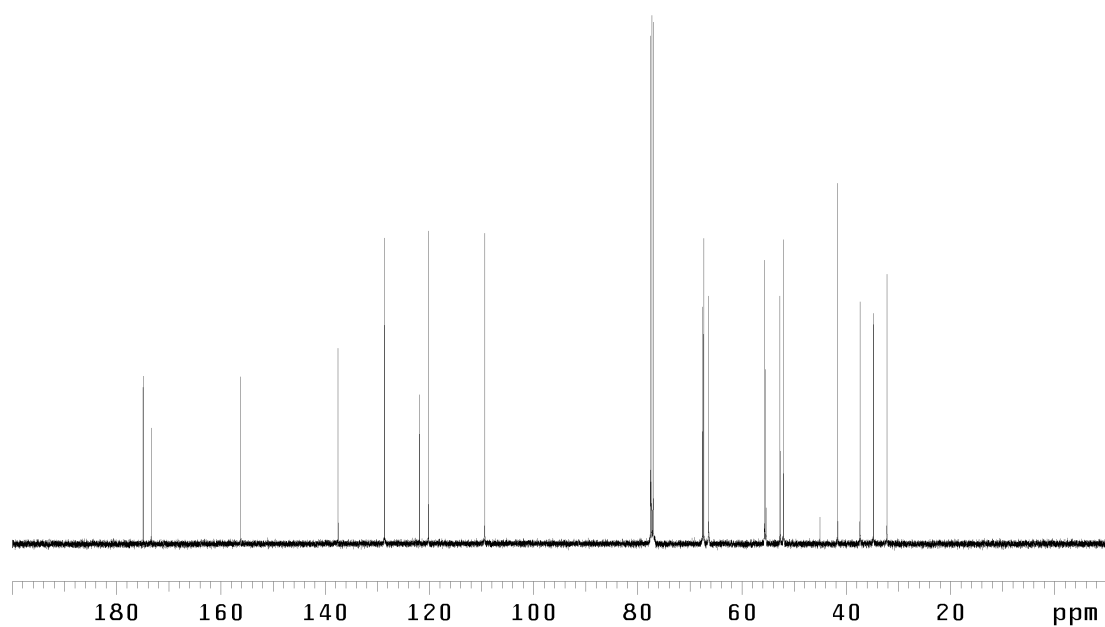


Figure 9.3.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of *N*-methyl amine **21**.

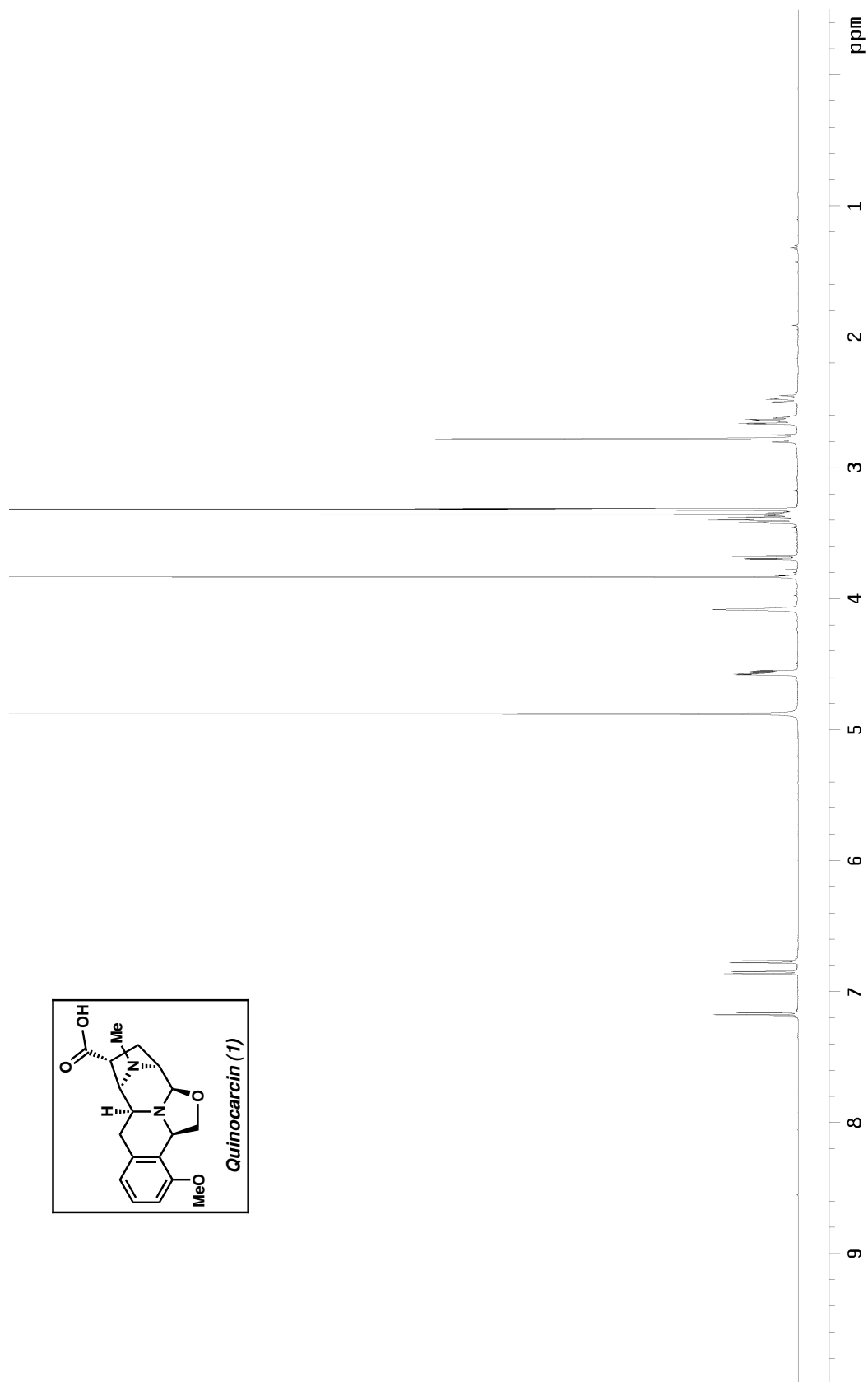


Figure 10.1.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ) of *(-)*-quinocarcin (**1**).

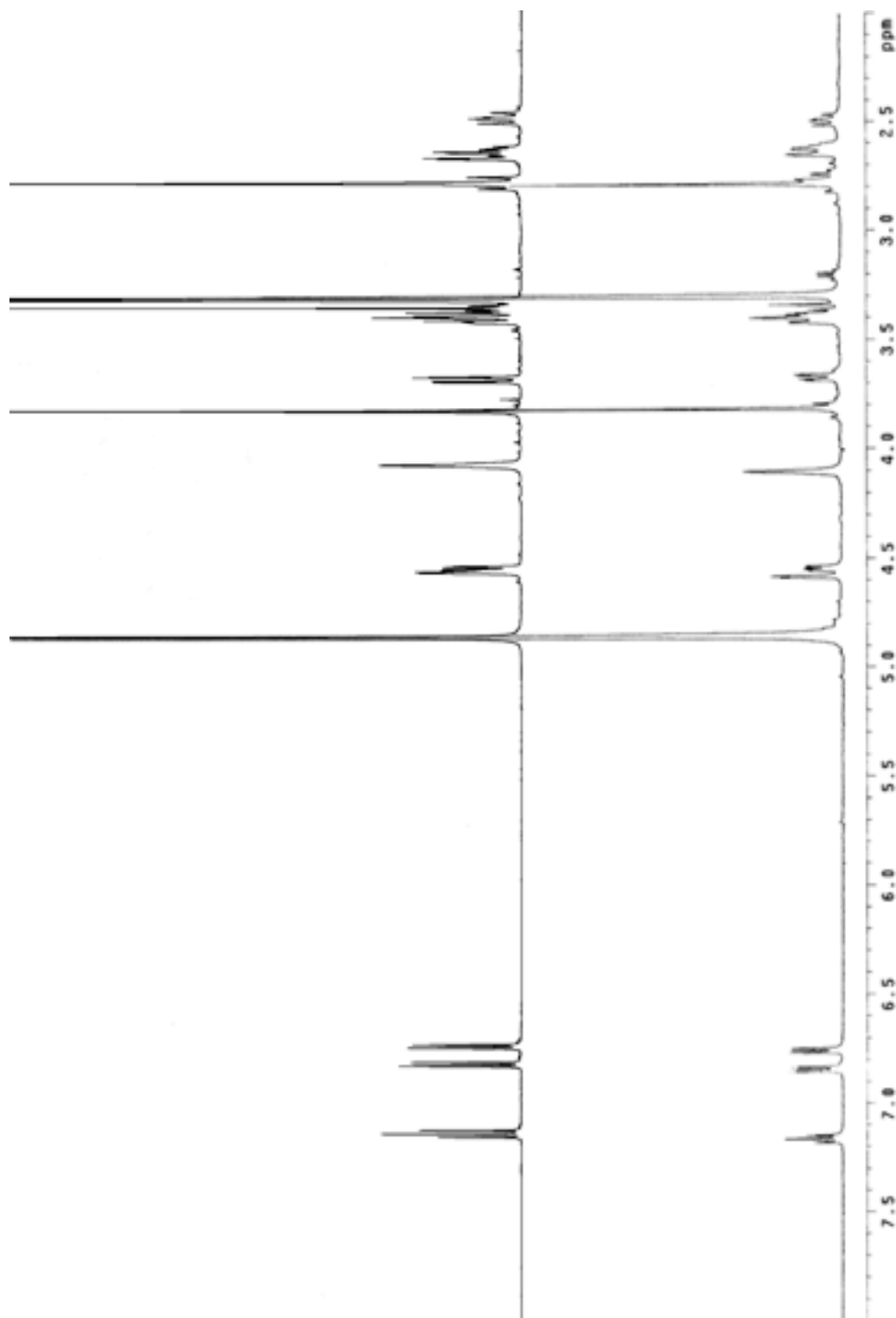
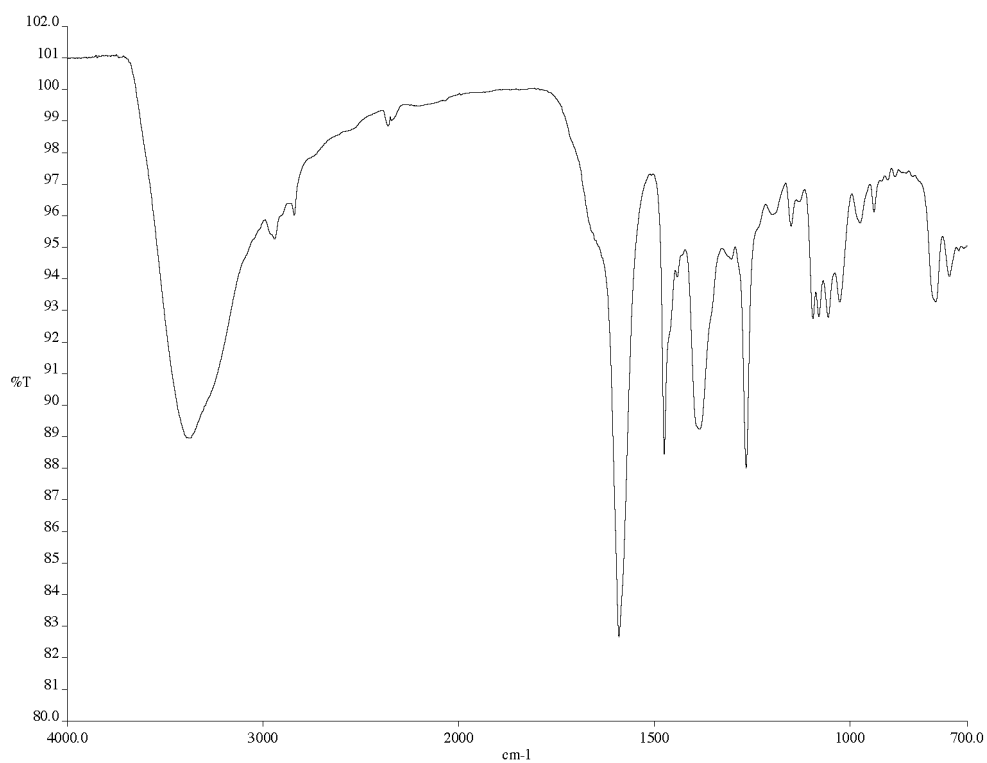
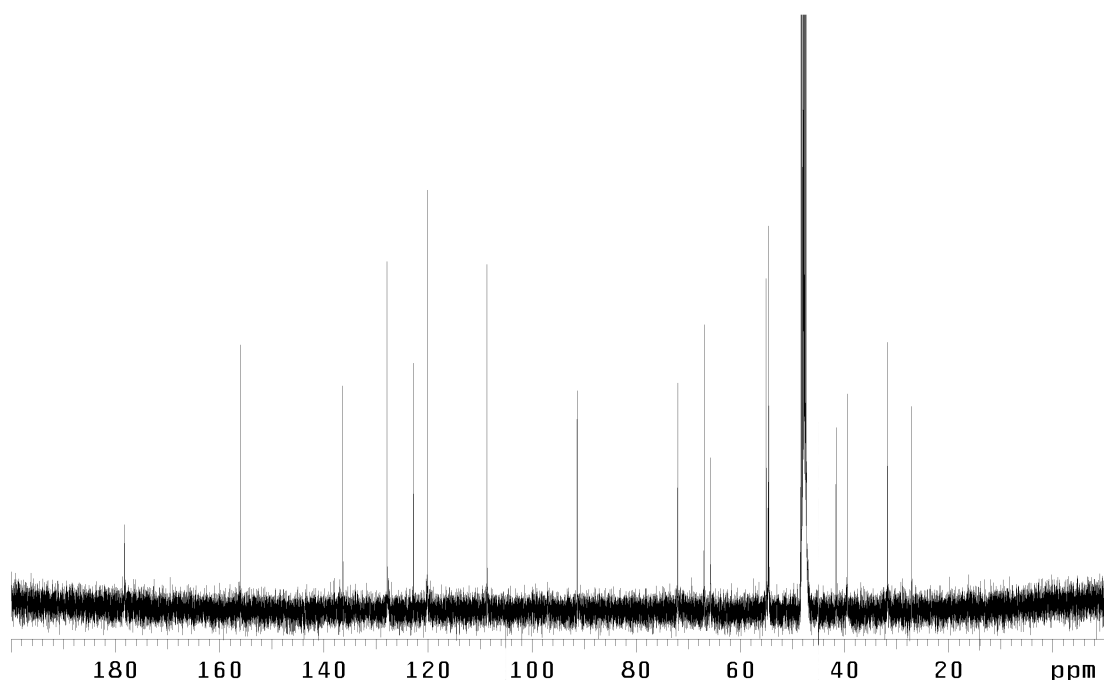


Figure 10.2. <sup>1</sup>H NMR comparison of synthetic (above) and natural (below) (-)-quinocarcin (**1**) (500 MHz, CD<sub>3</sub>OD).



*Figure 10.3.* Infrared spectrum (thin film/NaCl) of quinocarcin (**1**).



*Figure 10.4.* <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) of quinocarcin (**1**).

**Supplemental Table 1.** Comparison of  $^1\text{H}$  NMR data for synthetic and natural quinocarcin.

Synthetic (ppm)	Multiplicity	Natural <sup>7</sup> (ppm)	Multiplicity
7.17	t	7.16	t
6.85	d	6.84	d
6.76	d	6.76	d
4.57	d	4.57	d
4.55	dd	4.54	dd
4.07	br s (2H)	4.08	br s (2H)
3.82	s (3H)	3.82	s (3H)
3.68	dd	3.67	dd
3.43–3.33	comp m (2H)	3.41–3.35	m (3H)
3.39	dd		
2.79–2.74	m	2.79–2.74	m
2.77	s (3H)	2.77	s (3H)
2.64	dd	2.64	dd
2.64–2.60	m	2.63–2.59	m
2.46	dd	2.47	dd

**Supplemental Table 2.** Comparison of  $^{13}\text{C}$  NMR data for synthetic and natural quinocarcin.<sup>8</sup>

Synthetic (ppm) <sup>a</sup>	Natural <sup>7</sup> (ppm) <sup>b</sup>
179.5	174.9
157.2	157.2
137.6	137.0
129.1	129.1
124.0	123.8
121.3	121.3
110.0	110.0
92.6	92.1
73.2	72.3
68.2	67.9
66.9	66.8
56.3	56.3
55.9	55.9
55.7	53.4
42.8	40.6
40.7	40.3
32.9	32.5
28.3	27.3

<sup>a</sup>  $^{13}\text{C}$  NMR data measured at 125 MHz in  $\text{CD}_3\text{OD}$ .<sup>b</sup>  $^{13}\text{C}$  NMR data measured at 100 MHz in  $\text{CD}_3\text{OD}$ .

## References

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- (1) The fundamental reaction protocol for this dipolar cycloaddition is based on the pioneering work of Joule, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, 28, 2187–2190. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, 31, 4781–4782. (c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, 40, 331–347.
- (2) The specific experimental procedure for this dipolar cycloaddition is based on the previous synthesis of (–)-lemonomycin completed in our labs, see: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, 125, 15000–15001.
- (3) <sup>1</sup>H NMR analysis shows this crude material to be an 11:1 mixture of diastereomeric cycloadducts. The major diastereomer (**S-1**) is purified via subsequent recrystallization.
- (4) 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**17**) is prepared in three steps from 3-methoxyphenol, see: Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, 121, 5827–5828.
- (5) The ratio of dihydroisoquinolines (i.e., **18a:18b**) was determined by <sup>1</sup>H NMR.
- (6) The experimental procedure for the dissolving metal reduction is based on similar procedures carried out individually by Evans, Garner, and Zhu, see: (a) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, 108, 2478–2479. (b) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1992**, 114, 2767–2768. (c) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, 115, 10742–10753. (d) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, 130, 7148–7152.
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- (8) Fukuyama noted that the pH of the analytical solution had a dramatic effect on the chemical shifts in both the <sup>1</sup>H and <sup>13</sup>C NMR spectra of quinocarcin, accounting for observed differences between natural and synthetic spectra. See: Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, 110, 5196–5198.